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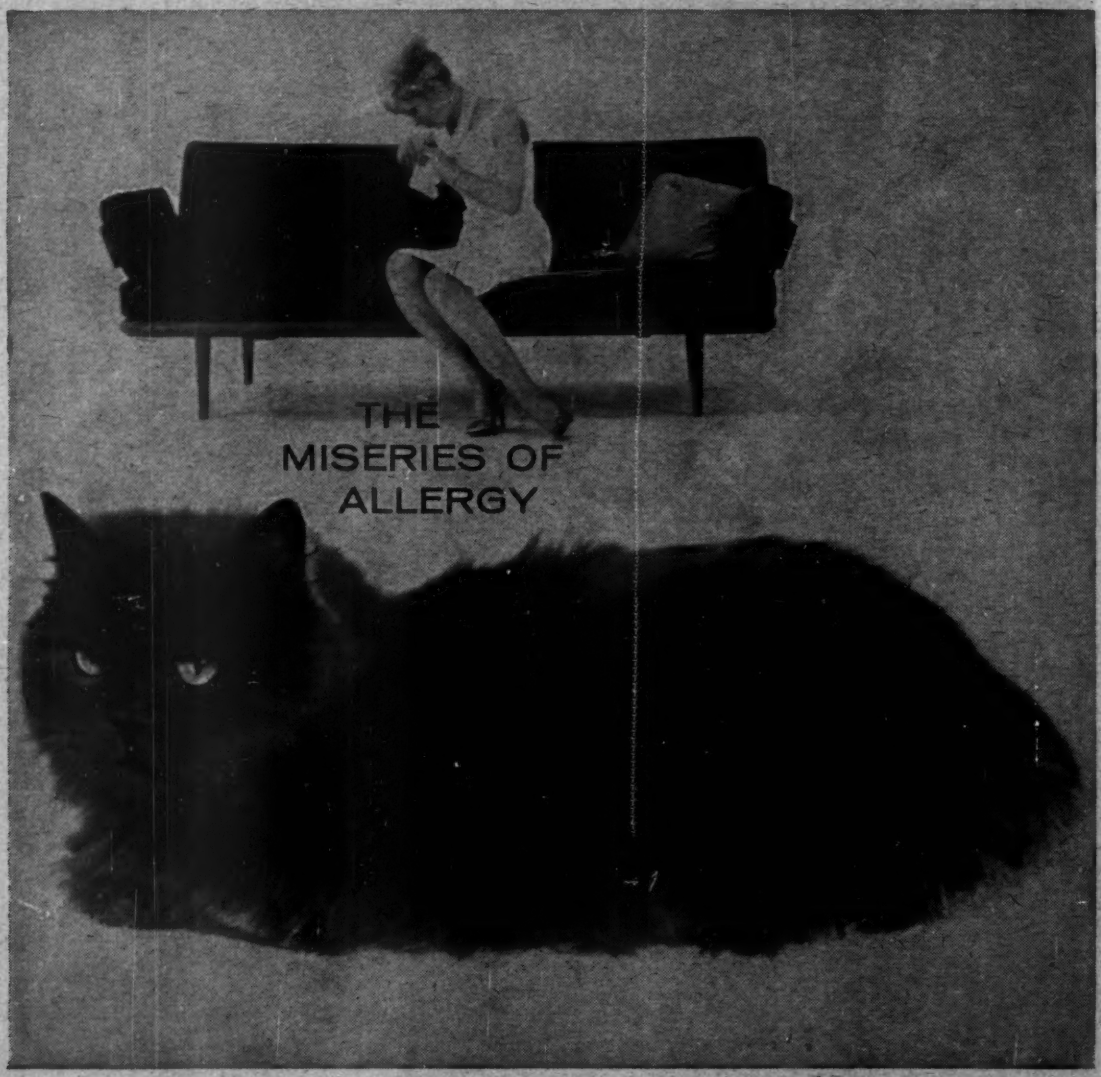

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY DECEMBER 31 1960

SEX DETERMINATION : DIAGNOSTIC METHODS*

BY

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In the early years of this century the entomologists McClung (1902) and Stevens (1905) recognized differences between the cells of the male and female of certain insects. During mitoses the female had either an additional or a larger chromosome than the male. This was relatively easy with chromosomes in small numbers, but their work has led the way to investigation of the more complicated chromosomal structure in the higher animals, including man. Quite early it was shown that when arranged in order of size the chromosomes fell into a series of pairs, and Painter (1924) settled what had been a 10-year argument by showing conclusively that in man the female was distinguished by the presence of a pair of like, XX, chromosomes, while the male had an unlike, XY, pair, the Y chromosome being much smaller than the X.

This arrangement is not universal. Although present in the mammals there are species of animals in which a chromosome is missing in the male, and even some, including the birds, where the difference is reversed, so that the males have the two X chromosomes.

Geitler (1937) made a further contribution to the study of sex by showing that in the water-skater, *Gerris lateralis*, the extra chromosomal material in the female sex chromosomes could still be detected after the cells had passed into the resting phase by the more intense staining of the nuclei. The observation that there was extra, deep-staining heterochromatin in the nuclei in the female was confirmed in the fruit-fly, *Drosophila melanogaster*, by Caspersson and Schultz (1940), using an elegant absorption-spectra technique, and in 1952 Hyden was able to apply similar methods to rabbit cells.

Nuclear Sex

The accidental discovery in 1949 by Barr and Bertram that in the neurones of the cat there was a nodule in the nuclei characteristic of the female started a new era in genetics. The later application of this observation to other tissues, including the human skin, made it possible to apply this experimental discovery to clinical medicine.

The nodule, described as being formed of deeply staining chromatin material, has a diameter of near 1 μ, and is most characteristically found applied to the inner surface of the nuclear membrane (Fig. 1).

*Read to the Section of Obstetrics and Gynaecology at the Annual Meeting of the British Medical Association, Torquay, 1960.

The discovery of a sex-specific pedunculated nodule, with a drumstick-like appearance, in the neutrophil, eosinophil, and basophil leucocytes, by Davidson and Smith (1954) and Davidson and Winn (1959), and the application of the original method to buccal mucosal smears by Moore and Barr (1955), provided two mutually confirmatory methods which have since been used widely in the investigation of cases of doubtful anatomical sex.

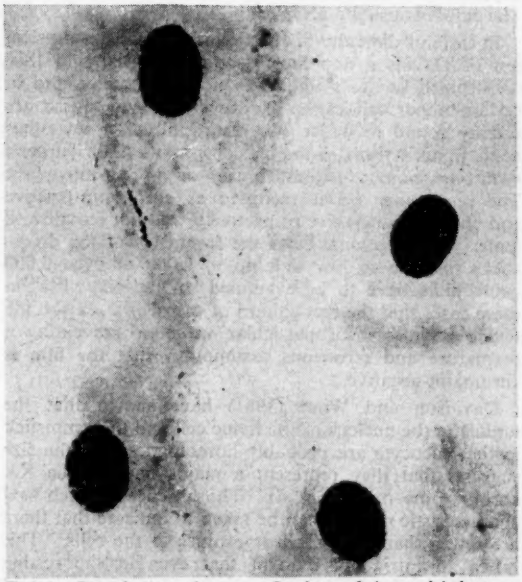

FIG. 1.—Buccal mucosal smear. In three of the nuclei there are the characteristic sex-chromatin nodules applied to the inner surface of the nuclear membrane. Female. (Haematoxylin and eosin. ×1,400.)

The neutrophil drumsticks, which have a dense chromatin head 1.5 μ in diameter, are characteristically separated from the rest of the nucleus by a thread-like connecting neck. Nodules with a short thick neck and sessile nodules, although nearly diagnostic of the female neutrophils, are more difficult to distinguish from other nodules found in both sexes (Figs. 2 and 3), but they can be used by an experienced observer in the recognition of the sex from blood films. Although only the drumsticks are sex-specific, all three types have a positive value, while the small sessile nodules and the thread-like

projections, which are commoner in the male, have a negative significance in the nuclear sex-screening test. In this test 100 or possibly 200 neutrophils are examined

FIG. 2.—Blood film. In the neutrophil there is one of the sex-characteristic drumsticks which mark a proportion of the female granulocytes (Jenner Giemsa. ×1,400.)

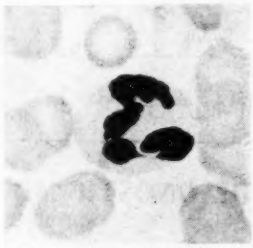

FIG. 3.—Blood film. In the neutrophil leucocytes there is a sessile nodule projecting from the end of the upper lobe of the nucleus. Such nodules are almost sex-specific and should be looked for when sexing blood films. Female. (Jenner Giemsa. ×1,400.)

for these features and the recognition of the sex depends upon the preponderance of one or other group. The result is usually clear-cut.

In cases of difficulty or special importance the classical test of Davidson and Smith should be used. In this, six drumsticks are sought. In normal females and in certain abnormalities, to be discussed later, these are usually found in under 300 neutrophils; on the other hand, in normal males and in such conditions as Turner's syndrome, none are found in 500 or more neutrophils. The results are better recorded as chromatin-positive and chromatin-negative respectively, and not female and male. In exceptional cases the frequency of the drumsticks may be so low that up to 2,000 or even 3,000 neutrophils have to be examined to find six. It is in these cases that the recognition of the nearly sex-specific sessile nodules is of particular value in preventing a premature and erroneous assumption that the film is chromatin-negative.

Davidson and Winn (1961) have shown that the nodule in the nucleus of the tissue cell and the drumstick in the leucocyte are probably homologues, and the size suggests that they represent a major part of the XX chromosome mass (Fig. 4). The absence of such sex-characteristic nodules can be taken to indicate that there are fewer than two X chromosomes in the cells. This raises an intriguing thought that even in the resting nucleus the chromosomes are not merely lost in a fluid state, but may be arranged in an orderly fashion. An interesting development, which if substantiated would cast doubt, not upon the diagnostic value of the sex chromatin, but upon the interpretation of its structure, comes from the work of Kosin and Ishizaki (1959), who showed that, although heterogametic, the females of the duck are still chromatin-positive.

Genetic Sex

In the past few years direct study of the chromosomes has been made possible by improved techniques. Through a combination of the bone-marrow-culture method developed in this country, particularly by Ford and Hamerton (1956) and by Ford *et al.* (1958), the use of colchicine to arrest mitoses in the mid-phase, and the loosening and spreading out of the chromosomes by the judicious use of hypotonic fluids as suggested by Hsu and Pomerat (1953), it has become possible to identify the individual human chromosomes.

The technical methods before this time had been so poor that even the traditional number of chromosomes in man, 48, was found to be wrong, and Tjio and Levan (1956) established the number as 46. Since then Tjio and Puck (1958) and Ford *et al.* (1959a, 1959b) in England, Lejeune *et al.* (1959) in France, and Fraccaro *et al.* (1959) in Sweden have been attempting to recognize the individual chromosomes, and have concluded that in the female the X chromosomes are probably the seventh pair of chromosomes in order of size and are metacentric—that is, when the chromosomes split longitudinally in diakinesis the two chromatids formed remain attached centrally (Fig. 5). The Y chromosome has also been recognized as one of the five small acrocentric

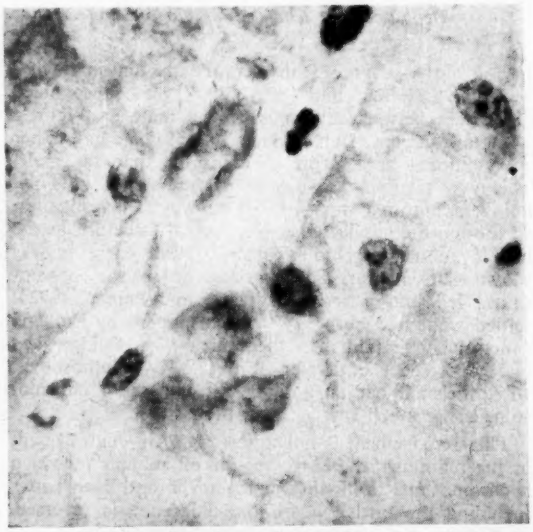

FIG. 4.—Section of liver tissue. In one of the sinusoids there is a neutrophil with a drumstick, and at the other end of the sinusoid there is a liver cell with an intranuclear sex-chromatin mass. Female. (Haematoxylin and eosin ×1,400.)

FIG. 5.—Squash preparation from marrow culture. The chromosomes in the process of splitting into chromatids, which are still attached to one another at their centromeres. This mitotic figure is from a female, and the X chromosomes can be recognized by their being about the seventh pair of chromosomes in order of size, and having an almost but not quite centrally placed centromere. (Feulgen stain. ×2,500.)

chromosomes—that is, with the chromatids attached terminally—in the male.

With the introduction of nuclear sexing the brilliant clinical deduction that anatomical females suffering from gonadal dysgenesis (Turner's syndrome) had not the XX chromosome structure, made by Polani *et al.* (1954, 1956) and Bishop *et al.* (1956) from the relatively high frequency of coarctation of the aorta and colour-blindness, was substantiated by finding that these "girls" lacked sex chromatin in their cells. From recent chromosomal studies by Ford and by Fraccaro this has come to have a further meaning: these "girls" are neither male nor female, but have the XO chromosome structure.

In parallel with these morphological developments the chemists have successfully analysed the physico-chemical structure of the chromatin itself. The essential constituent deoxyribonucleic acid has been shown to have in the central part of its double helical molecule a balanced arrangement of the purine and pyrimidine bases, adenine and guanine, thymine and cytosine. The importance of this structure lies in the almost infinite number of variations provided by changes in the order in which the 3,000 or more bases are arranged. This is believed to provide the mechanism for carrying the hereditary pattern—that is to say, a "gene" is really a specific arrangement of the bases at a point on the deoxyribonucleic acid molecules.

This hereditary configuration determines in turn the detail of the structure of the more simple form of nucleic acid, ribonucleic acid, which is intimately connected with the formation of protein, and is present more abundantly in the cytoplasm than in the nuclei of the cells. Thus it seems that the ribonucleic acid passes on the hereditary structural information stored in the deoxyribonucleic acid by acting as the template from which the amino-acid molecules in the specific proteins, including the enzymes, are arranged. Finally, these enzymes which are formed play an all-important part in every cellular function, including the formation of hormones and probably also the reaction of the tissues to the hormones.

In this way the hereditary pattern, the genes, controlling sex is represented in the nuclei of every cell in the body, and can influence the development of the tissues and their reaction to normal and abnormal hormonal stimulation. The inheritance of this sex pattern, the genetic sex, is apparently the result of a balance between the genes having a male influence, which are scattered on the autosomes, and those having a female influence, concentrated on the X chromosomes. Normally the genetic sex agrees with the chromosomal sex—that is, whether in mammals the individual bears the like XX pair or the dissimilar XY pair of chromosomes—and as in theory this determines whether the amount of heterochromatin present is sufficient to form a sex-specific nuclear nodule or not, it has been believed that the nuclear sex must be directly linked to the chromosomal sex. Despite the new work by Ohno *et al.* (1959) suggesting that only one X chromosome forms the chromatin nodule, and the difficulty, already mentioned, which has been aroused by Kosin and Ishizaki (1959) finding sex chromatin in female ducks, it still seems that there must be a basic linkage even if it is more complicated than formerly anticipated.

Normal females are thus chromatin-positive and normal males chromatin-negative, but in abnormalities of sexual development this relationship is not always maintained, and particularly it must be realized that the nuclear sex does not distinguish between XXY, XXX, and XX, nor between XO and XY.

Somatic Sex

Gonadal Sex.—The specific development of the cortex of the primitive gonad to an ovary or of the medulla to a testis, although determined genetically, is mediated through cellular and hormonal factors. The arrival of the germinal cells in the gonadal blastema after their migration from the region of the yolk sac seems to initiate the development, but embryonic hormones, probably produced by the developing pituitary gland, also play an important part (Jost, 1950). This has been confirmed by the sex-reversal experiments on very immature opossums taken from the marsupial sac of the mother (Burns, 1956).

Development of the Sex Ducts and External Genitalia. — The gonads influence the subsequent development of the genital tracts from the sixth to eighth weeks of embryonic life onwards. The developing testis seems to have a positive action, causing the regression of the mesonephric (Müllerian) in favour of the paramesonephric (Wolffian) duct; the male type of development of the urogenital sinus; enlargement of the genital tubercule; and secondary fusion of the genital folds to form the penile urethra. In contrast the ovary is relatively inactive, and Jost (1950) has shown that if all gonadal tissue is removed, in either sex, the subsequent development of the genital tracts follows the female pattern. At this stage abnormal suprarenal

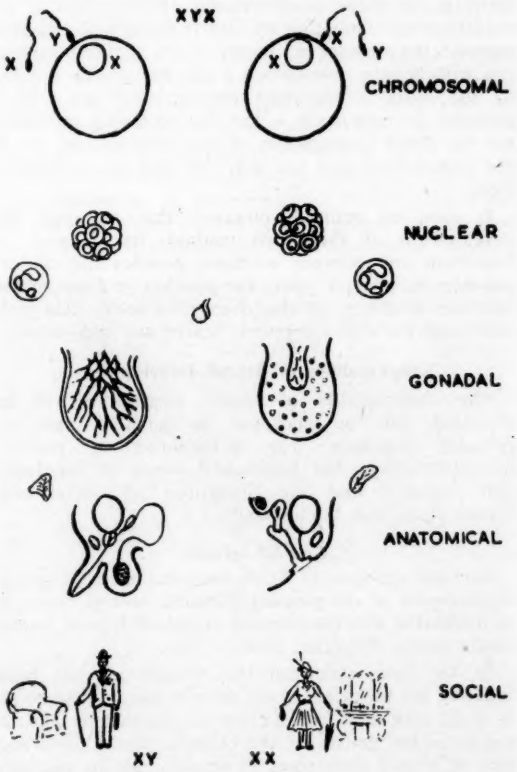

FIG. 6.—Diagrammatic representation of the various levels of sex representation.

hormones can produce sufficient disturbance to cause difficulty in recognizing the anatomical sex (Prader and Siebenmann, 1958).

Development of the Secondary Sex Characteristics.—While there is a fundamental agreement between the genetic, chromosomal, nuclear, and anatomical levels of sex development, the subsequent maturation of the structures and the formation of the secondary sex characteristics, although greatly influenced by the gonadal hormones, also involves other less directly connected factors. These include pituitary and suprarenal hormones.

Social Sex

The anatomical or somatic sex, and particularly the structure of the external genitalia, has a dominating influence upon the development of those physical and mental qualities expressing themselves in dress, friendships, choice of occupation, and hobbies, by which we recognize the social sex. Even in normal individuals there is considerable variation in the degree of expression of social sex, but in some the aberration exceeds the wide limits we have set, and occasionally the outlook is so distorted that the individual cannot fit into any ordinary form of community life (Fig. 6).

Abnormalities of Sex

Although in the vast majority of people there is agreement throughout the sexual structure, every variety of discrepancy may be met in abnormal cases. The determination of the nuclear sex, a relatively easy procedure, is an important tool in investigating these developmental abnormalities if its usefulness and limitation are clearly recognized. It only indicates the presence or absence of two X chromosomes, but with certain reservations it can be used as a guide to the more fundamental chromosomal sex. It is essential to have such a test for screening purposes, for the direct investigation of the chromosomal sex is too complicated and can only be used in exceptional cases.

It must be realized, however, that although the development of these two methods has formed an important link between academic genetics and clinical practice, we are not yet in the position to examine the intimate structure of the deoxyribonucleic acid and determine the ultimate genetic sex of any individual.

Abnormalities of Sexual Development

The abnormalities of sexual development to be discussed can be classified as gonadal agenesis, gonadal dysgenesis, true hermaphroditism, pseudohermaphroditism, the hyposexual states of impotence and frigidity, and the distortions of social sex, transvestism, and homosexuality.

Gonadal Agenesis

Gonadal agenesis, in which there has never been any development of the gonadal blastema, will of necessity be associated with the negative or female type of bodily configuration (Overzier, 1957).

In the cases described the nuclear sex has been negative, but the origin of the disorder is not understood. It could arise as a local failure of growth affecting the region of the gonad, or the blastema could form and then at a very early stage in development be partially or here totally destroyed by a noxious substance passing from the mother to the foetus. This substance could come from a hormonal disturbance or, as Witschi *et al.* (1957) have suggested, a tissue incompatibility, comparable to that in erythroblastosis foetalis.

Gonadal Dysgenesis

Gonadal dysgenesis occurs in two forms, Klinefelter's and Turner's syndromes, two very interesting disturbances of sexual development. In the former the gonad is a maldeveloped testis, in the latter a maldeveloped ovary.

A minority of the cases of both conditions appear to arise as a simple local anomaly affecting the gonad, with no discrepancy between the nuclear, gonadal, and anatomical sex. In the majority, however, there is a striking aberration. In such cases of what is sometimes called true Klinefelter's syndrome, the nuclear sex is chromatin-positive despite the completely male anatomical structure, including the presence of testes. After puberty, however, the testes fail to mature properly and most of the tubules are found to be degenerate. Those embedded in the large masses of degenerate interstitial cells tend to retain their size and lining of Sertoli cells, but the remainder undergo a rather characteristic type of hyalin degeneration (Fig. 7).

FIG. 7.—Tissue section. The testicular tissue from Klinefelter's syndrome showing the characteristic hyaline degeneration of the tubules and the massing of the Leydig cells. (Haematoxylin and eosin. ×100.)

Occasional areas of spermatogenesis have been found, and even a few cases, including one of my own (Davidson and Smith, 1958), have had spermatozoa in the seminal fluid. So far no instance of a sufferer from Klinefelter's syndrome having fathered a child has been found.

In the cases of what might be termed true Turner's syndrome a similar discrepancy is found, except that it is in the opposite sex. Here the cells are chromatin-negative yet the anatomical structure is feminine, even to the positioning of the gonads. These, however, are poorly developed and usually composed entirely of ovarian stroma, although in one personal case there were some ill-defined cell-cords with germinal cells (Davidson and Winn, 1959) (Fig. 8), and even ova have been described by Atria *et al.* (1948).

Colour-vision studies in these syndromes by Polani *et al.* (1958) have suggested that, despite the gonadal structure, nuclear sexing is still correct in indicating the presence of two X chromosomes in Klinefelter's

FIG. 8.—Tissue section. Ovarian tissue in Turner's syndrome. A few undeveloped germinal cells are to be seen in a cell cord or tubular remnant buried in the ovarian stroma. (Haematoxylin and eosin. ×100.)

syndrome and, conversely, only one in Turner's syndrome. Recent chromosomal analyses by Ford and Jacobs (Jacobs and Strong, 1959) have confirmed this, but have explained the discrepancy by revealing an XXY structure in Klinefelter's syndrome and an XO structure in Turner's syndrome. Cases of Klinefelter's syndrome could thus be regarded as males with an additional X chromosome, or females with an added Y, and cases of Turner's syndrome as females lacking an X chromosome, or males lacking a Y chromosome.

Such chromosomal patterns are believed to arise through non-disjunction of the sex chromosomes at meiosis—that is, during the formation of the gametes in either the father or the mother. During either the first or the second division, instead of the sex chromosomes separating, both go to one nucleus and none are left for the other. If the maldivision occurs in the father, either a spermatozoa-carrying XY or one lacking any sex chromosome could unite with a normal ovum carrying one X and result in a child with, in the former instance, Klinefelter's, and, in the latter, Turner's syndrome. With non-disjunction in the mother there are two further possibilities—the union could also produce XXX or YO zygotes. If non-disjunction takes place at the first meiotic division it would seem that Klinefelter's and Turner's syndromes should occur with the same order of frequency, and more commonly arise from the father (Fig. 9). This does not appear to be the case, for in practice, according to Moore (1959), Klinefelter's syndrome is the commoner, and Stern (1959) believes that it is more often due to non-disjunction in the mother. So that non-disjunction at the second meiotic division must also be considered (Fig. 9). A sterile female has recently been found to have the third viable product of non-disjunction, the XXX structure. Aberrations during early mitoses in the zygote could produce mosaicism.

Why this mechanism of non-disjunction should cause the gonadal dysgenesis is not clear. It may be that the abnormal chromosomal complement interferes with the migration of the germinal cells or that the enzymes formed from the abnormal deoxyribonucleic acid complement are inimical to the development of the gonad.

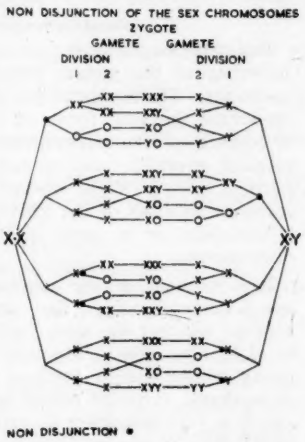

FIG. 9.—A diagram to show the effect of non-disjunction during the first or second reduction divisions in the formation of the gametes. The possible zygotes which result from the union of a product of non-disjunction and a normal gamete are arranged in the centre of the diagram. These are the combinations which give rise to gonadal dysgenesis and certain allied conditions (Klinefelter's syndrome, XXY; Turner's syndrome, XO; superfemales, XXX; and lethal combinations such as YO and XYY).

True Hermaphroditism

In true hermaphroditism there can be no simple agreement between the nuclear and gonadal sex, as both testicular and ovarian tissues are present (Fig. 10). Although both chromatin - positive and chromatin-negative forms occur, most of the cases studied have been chromatin - positive. In these the frequency of the neutrophil drumsticks and of the tissue nodules is within the normal limits, suggesting that the condition is not a mosaic state. Barr (1955) has also confirmed this by finding that the skin from both sides of the body had the same chromatin structure and was not male and female as in gynandromorphism in animals.

A form of mosaic state has been met in man in the blood chimeras. In these binovular twins fusion of the placentae at an early stage of development had allowed an exchange of marrow elements, resulting in a mixing

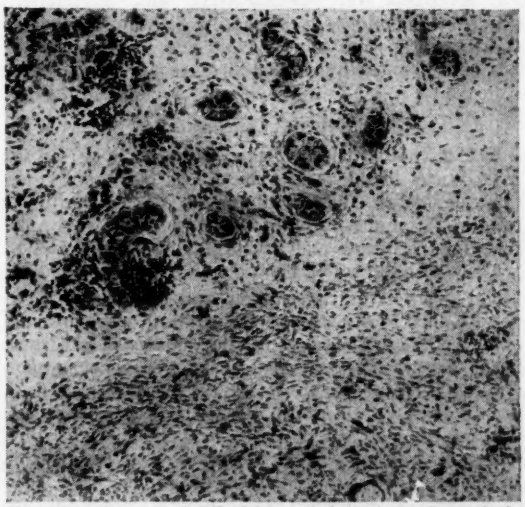

FIG. 10.—Tissue section. The junction between the testicular and ovarian tissue in the gonad from a true hermaphrodite. (Haematoxylin and eosin. ×100.)

of the blood groups and both male and female leucocytes (Davidson *et al.*, 1958). Except for the lack of genital abnormalities, this condition is comparable to the freemartin state in cattle.

Pseudohermaphroditism

Pseudohermaphrodites are classified as male or female according to the gonads present, regardless of other variations. The nuclear sex and the gonadal sex are in agreement in this form of intersex, but there is divergence of the development of the genital ducts, external genitalia, and secondary sex characteristics, ranging from a slight distortion of the genitalia to complete reversal of the anatomical structure, so that it simulates or is even identical with that of the opposite sex.

It is perhaps in the relatively common group of pseudohermaphrodites that nuclear sexing has its greatest use, but the mere fact that by it we are able to determine with reasonable certainty the type of gonad present should not lead us prematurely into the more drastic forms of plastic surgery. Even at birth—and it is very important to make the decision as soon as possible—it may be unwise to attempt to correct the genital defect, and, once the child has been reared for a time in the " wrong " sex, the social sex adopted may have become so deeply rooted that it would be meddlesome to interfere.

Psychological Disturbances

Although the social sex is mainly dependent upon the anatomical sex, rearing has an important effect and there is an intricate psychological background to the errors. Social sex may be so poorly developed or so disturbed as to result in impotence or frigidity, even in the absence of any anatomical error or any discrepancy between the gonadal, nuclear, and genetic sex. A severe aberration of the mental outlook results in those reversals of the social sex known as transvestism and in homosexuality. These disturbances may have some genetic predisposition, but this does not usually show as any morphological alteration in the sex chromosomes and the nuclear sex is in keeping with the gonads and the anatomical structure. Only in the rare instances of an admixture of homosexuality and Klinefelter's syndrome, mentioned by Davidson, Siebenmann, Bishop (see Davidson and Smith, 1958) and Overzier (1958), has any abnormality of the chromosomes been found.

General Conclusion

The discovery of the method of recognizing the sex from nuclei in the resting-phase cells has opened new fields of interest, and the stimulation it has given to the new work on the chromosomal structure has for the first time formed a real bridge linking the theories of genetics with the practical problems of clinical medicine.

This work is only beginning, and is undoubtedly to be extended. Already we recognize a chromosomal abnormality as the cause of mongolism. There must be also other morphological changes, dependent upon chromosomal abnormalities, whose significance has not been recognized. Another attack upon these problems is being made by the physical chemists who are painstakingly analysing the structure of complex organic substances. The abnormal haemoglobins have been elucidated by Ingram (1957), protein structures are becoming understood, and there are hopes of advances in the study of deoxyribonucleic acid, the key to inheritance.

Summary

While the determination of the nuclear sex is of the greatest practical value in the group of pseudohermaphrodites, it must be regarded as a fundamental investigation in anomalies either affecting the genitalia or with a sex preponderance. Although it only marks the presence, or absence, of two X chromosomes, and must be interpreted with this in mind, it is still the test of choice in clinical work while chromosomal studies remain as a research tool.

The buccal-mucosal-smear and blood-film techniques are mutually confirmatory examinations, and in cases of difficulty or special importance both should be made.

Investigations of the chromosomal structure of the dividing marrow cells has yielded results of the greatest importance in the field of abnormalities of the sex organs. The discovery of the abnormal XXY structure in Klinefelter's syndrome and of XO in Turner's syndrome has gone a long way to explain the discrepancy between the gonadal structure and the nuclear sex in these conditions, and has transformed theoretical genetics to a subject with practical application.

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INTERSEX STATES*

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It is obviously very important, psychologically, to make a firm and accurate diagnosis of the correct sex well before puberty. In the future some of these conditions and their problems may be rarities. In this paper the various types of sexual aberration which may be seen by the gynaecologist at the present time are discussed.

At this stage it is best to establish the criteria of sex, as so many factors are involved. Firstly, there is the physical status, observed by examination of both external and internal genitalia and the gonads, the absence or nature of the secondary sexual characteristics, and the menstrual history. Then both the sex psyche and the social sex of the patient are of great importance, and, in addition, we now have the opportunity of determining the presence or absence of sex chromatin in somatic nuclei, and in some centres of actually recording the chromosomal pattern. It is only after careful consideration of all these factors that an ultimate decision can be made. Generally speaking, treatment, if required, must be chiefly influenced by the social and psychological sex of the patient. However, it is probably unethical to consider these latter factors alone, without the support of at least some complementary physical or genetic evidence.

The various genetic aberrations have already been described, and it is suggested that two X chromosomes are necessary for the development of the normal female gonadal cortex, and that a Y chromosome is essential for development of the male gonadal medulla (Stewart, 1959a). This normally occurs in the embryo during the fourth to sixth week, and before this time the gonadal anlage is an indifferent organ.

Jost (1953) showed that rabbits, whether genetically male or female, developed female internal and external genitalia if the gonads were removed during early embryonic development. Thus in the absence of gonads a female phenotype develops regardless of the chromosomal sex of the individual. Even when the sex has been genetically determined as male with XY chromosomes, other factors, genetic or non-genetic, may be necessary to ensure sexual differentiation into the male phenotype, and eunuchoid females have been reported with XY chromosomes (Harnden and Stewart, 1959).

In addition to the sex chromosomal changes and other genetic possibilities, the development of the external genitalia of the female embryo of 11–20 weeks is influenced by abnormal androgens, whether these are of endogenous adrenal origin due to a metabolic error (Jailer, 1953) and apparently due to an autosomal recessive factor (Stewart, 1959b), or whether they are given to the mother in the form of androgens or progestogens in early pregnancy. In such cases the ovaries are merely suppressed, but the external genitalia are remarkably virilized and sometimes ambiguous.

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Sexual anomalies can be classified as follows:

Congenital Conditions

1. Aberrations due to chromosomal defects:
   - (*a*) True hermaphrodite, XX/XY or mosaics.
   - (*b*) Gonadal dysgenesis with a male phenotype. Klinefelter XXY.
   - (c) Turner's syndrome, XO or XX.
   - (*d*) Gonadal dysgenesis, XO, XX, or XY with a female phenotype.
   - (*e*) Superfemale or metafemale, XXX.
2. Other genetic defects:
   - (*a*) Testicular feminization or male pseudohermaphrodite, XY.
   - (*b*) Male with undescended testicles, hypospadias, and female micturition brought up as a female, XY.
3. Embryonic virilization:
   - (*a*) Pseudohermaphrodite, XX.
   - (*b*) Steroid-induced pseudohermaphrodite, XX.
   - (c) Adrenal virilism after differentiation of external genitalia, XX.

Post-natal Conditions

(*a*) Adrenogenital syndrome — hyperplasia; tumour — adenoma, carcinoma — XX.

- (*b*) Stein–Leventhal syndrome, XX.
- (*c*) Constitutional virilism, XX.
- (*d*) Male-type tumour, XX: arrhenoblastoma; hilar-cell tumour; adrenal rest tumour.

Steroid-induced pseudosex

- (*a*) Pseudofemale, XY.
- (*b*) Pseudomale, XX.

True Hermaphrodites

These are rare, only about 60 cases having been described, and in about 70% the social sex was male. Diagnosis can be made only by gonadal biopsy. Hinman (1935) describes three types: (1) bilateral, with an ovary and a testis on both sides, or bilateral ovotestes; (2) unilateral, with testis and ovary separate or united on one side and an ovary or testis on the other; and (3) lateral, or alternating, with a testis on one side and an ovary on the other.

It is not surprising that the variations of the clinical state are many.

Arneaud, Annamunthodo, Pinkerton, and Cole (1956) described the case of an apparent feminized male of 18 years whose nuclear sex was shown to be female; he was shown to have one ovary and an ovotestis. Barr (1955) determined the nuclear sex of nine such patients and found six with female-type nuclei and three with absent sex chromatin.

Harnden and Armstrong (1959) investigated a masculine female of 70 years with one ovotestis and found 46 chromosomes with XX sex chromatin pattern, and most tissue nuclei were chromatin-positive. However, Stewart (1959b) stated that true hermaphrodites might be mosaics of XX and XY or XXY gonadal tissue, but their status is still not clear.

Gonadal Dysgenesis

In males there is every gradation from complete agenesis of Leydig cells and tubules with eunuchoidism to the apparently normal virilized male with some degree of tubular dysgenesis, and azoospermia or oligozoospermia. The syndrome described by Klinefelter, Reifenstein, and Albright (1942) consists of gynaecomastia, small testes, absence of spermatogenesis,

and an increased urinary excretion of follicle-stimulating hormone. Heller and Nelson (1945, 1948) subdivided the condition into three main types. At one end of the scale there were eunuchoid features—that is, dysgenesis of Leydig cells and tubules; these showed little gynaecomastia, whereas if the Leydig cells were relatively unaffected there was gross gynaecomastia. All these testes show small tubules with absent spermatogenesis, but hyalinization of the basement membranes is not an invariable finding. A large majority of these cases are chromatin-positive XXY, but some are chromatin-negative XY (Grumbach, Blanc, and Engle, 1957; Stewart, Ferguson-Smith, Lennox, and Mack, 1958). They are all sterile, and the chromatin-positive cases made up 3% of all patients attending a male infertility clinic (Ferguson-Smith, Lennox, Mack, and Stewart, 1957). So, too, in the female, ovarian dysgenesis can be associated with varying degrees of ovarian defect. Turner's syndrome is perhaps the best-known form and usually shows complete ovarian agenesis, sex-linked with other genetic defects, such as dwarfism, web-neck, cubitus valgus, abnormal facial or cranial development, and anomalies of the cardiovascular or urogenital systems. These usually have a chromosome pattern XO, but some may be XX.

However, pure gonadal dysgenesis may be seen without dwarfism and other sex-linked defects. The clinical features will naturally depend on the degree of ovarian deficiency. Thus one may see a tall eunuchoid female with absent secondary sexual characteristics and a hypoplastic uterus, or a girl with immaturely developed breasts and nipples, with primary amenorrhoea or a short-lived menstrual history, followed by amenorrhoea or oligomenorrhoea or possibly only infertility due to failure of ovulation.

Sex chromatin may be absent in the nuclei of some cases or present in a smaller proportion than in the normal female.

In a case recently described by Harnden and Stewart (1959) a tall eunuchoid girl of 19 with primary amenorrhoea, absent breasts, and scanty pubic and axillary hair was found to have normal external genitalia and uterus, but no gonads were palpated. Oestrogen withdrawal bleeding was induced, *but* she had no sex chromatin and her chromosome pattern was XY. They state that in the absence of gonads a female phenotype develops regardless of the chromosomal sex of the individual and that the possession of a Y chromosome is not sufficient to ensure the development of a male phenotype.

The Superfemale

Only one case has so far been reported (Jacobs, Baikie, Court Brown, MacGregor, Maclean, and Harnden, 1959b). Their patient was a woman of 35 who presented with secondary amenorrhoea. Menstruation started at 14 and occurred irregularly every two to three months until 19. Her breasts, vulva, vagina, uterus, and cervix were all small. Ovarian biopsy showed a normal stroma but only two follicles and no corpora albicantia.

Buccal smears showed a greater proportion (71%) of nuclear chromatin bodies than in the normal woman (36–51%) and some of the nuclei contained two chromatin bodies. Chromosome analysis revealed a count of 47 chromosomes with an XXX constitution. The term "metafemale" is preferred for this condition by Stern (1959).

Testicular Feminization, or Male Pseudohermaphrodite

These patients may have well-developed breasts, scanty pubic and axillary hair, and normal external genitalia, but there is usually an absent or very short vagina and an absent or vestigial uterus. They may present because of primary amenorrhoea or with herniae or labial swelling. There is an absence of sex chromatin in the buccal smears, and at operation the gonads are quite obvious testes, which either are histologically normal with some degree of spermatogenesis or they may show the cryptorchid pattern.

These gonads produce female hormone and if they are removed the breasts atrophy and menopausal symptoms ensue (Goldberg and Maxwell, 1948).

In four such cases a chromosomal sex of XY pattern was demonstrated by Jacobs, Baikie, Court Brown, Forrest, Roy, Stewart, and Lennox (1959a) who describe them as sex-reversed males. The male with undescended testicles and hypospadias who has been brought up as a girl also has XY chromosome pattern and other signs of virilization. It is probable that these will usually be recognized before adult life.

Pseudohermaphroditism

In these cases there is a large phallus with a persistent urogenital sinus. Precocious puberty with virilization occurs, with the result that growth is rapid at first, but ceases prematurely with early closure of the epiphyses. The voice is deep, the body hirsute, and there is no breast development, and primary amenorrhoea is the rule. The ovaries and uterus are small but normal in position. There is often a family history of endocrine disease, and siblings may be affected (Broster, Patterson, and Camber, 1953). In all the cases I have seen the social and psychological sex and the nuclear sex have been female. If the adrenal disturbance occurs after the fourth month of foetal life, when the external genitalia have developed, the child is born with hypertrophy of the clitoris but without a urogenital sinus (Wilkins, 1957). The excretion of 17-ketosteroids is always high, and it rapidly falls on the administration of prednisolone or dexamethasone, given to suppress the adrenal cortex. If this treatment is given early and continuously before puberty the patient will develop into a normal female with regular menstruation, and several have given birth to normal children.

Therapeutic or Steroid-induced Pseudohermaphrodite

Women who have received androgen or progestogen therapy for repeated miscarriages or haemorrhage during early pregnancy may give birth to female babies with congenital defects of the external genitalia similar to those of the pseudohermaphrodite (Wilkins, Jones, Holman, and Stempfel, 1958; Hayles and Nolan, 1958; Nellhaus, 1958; Moncrieff, 1958).

Post-natal Conditions

All this group show some degree of virilization and a normal XX chromosomal pattern. In the adrenogenital syndrome virilism occurs, and at any age after birth. The clinical picture will obviously depend on the time of onset before or after puberty and the nature of the source and rate of production of androgens—that is, hyperplasia and simple or malignant tumour of the cortex. Before puberty the phallus will be quite large, and there will be an absence of female sex characters

and varying signs of precocious puberty and virilization. After puberty defeminization merging into virilization occurs and the clitoris rarely exceeds 1 cm. in diameter.

Virilizing ovarian tumours—the arrhenoblastoma, hilar-cell tumour, or adrenal rest tumour—all secrete androgens of some kind, although the 17-ketosteroids may not always be elevated. The general picture is usually seen in adult life, and is one of defeminization and virilization (Foss and Leverton, 1959).

Two other conditions deserve mention—constitutional virilism (Ferriman, Thomas, and Purdie, 1957), which is a common condition and may be familial or racial, and, finally, the Stein–Leventhal syndrome of hirsuties, obesity, amenorrhoea or oligomenorrhoea, and polycystic ovaries and infertility, which again probably occurs more often than is realized (Bailey, 1959).

The pseudofemale *was* a normal male in every respect before his conversion into an apparent female by means of massive and continued endocrine therapy and plastic surgery.

Similarly, the pseudomale is a hirsute well-muscled person who has been treated for years with androgens and usually had bilateral mastectomy and possibly plastic surgery to the external genitalia. It is not so easy for these patients to arrange for an oophorectomy or hysterectomy, and there is always the possibility that some gynaecological condition may arise. I know one such person who menstruates from time to time through her penile tube graft if she omits continuous androgen therapy.

Now, as Cawadias (1959) has reminded us, sex is a matter of total personality, dependent on the psychological personality as well as the genes, gonads, genital organs, and endocrines. Thus the management of these cases may involve considerable care and responsibility.

In Canada, Moore (1959) has determined the nuclear sex in 3,700 newborn infants, about equally male and female anatomically. Five anatomical males showed the presence of female nuclear chromatin. By the use of this simple screening test as a routine, it would be possible then to investigate the true chromosomal sex of babies in a doubtful category, and this would facilitate their correct upbringing, and treatment if necessary.

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TREATMENT OF RENAL FAILURE IN A UNIT WITH FACILITIES FOR HAEMODIALYSIS (TWIN-COIL ARTIFICIAL KIDNEY)

RESULTS WITH 80 PATIENTS

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Owing to the many and varied causes of acute renal failure, clinicians in practically every branch of medicine and surgery are faced from time to time with the problems of treatment of this condition. Conservative management of acute renal failure in the last 10 years has greatly improved results. It is now clear that haemodialysis with an artificial kidney is an important adjunct to treatment.

Since June, 1957, we have employed an artificial kidney (Kolff twin coil) at this unit. We give a brief survey of the treatment of patients admitted to the unit during the first two years since haemodialysis was available. No previous results with this type of artificial kidney have been published in this country apart from a short summary (Jackson, 1958). During the two-year period 78 patients have been admitted and 88 dialyses performed on 57 of them. A further two patients were dialysed once each in their own hospitals. The patients, 75% of whom were civilians, have been referred from over a wide area, mainly from the Midlands, South of England, and Wales.

In any unit admitting patients primarily for the treatment of renal failure, a considerable number will be found eventually to be in the terminal phase of a chronic renal disease, or to have an acute irrecoverable renal lesion, such as bilateral cortical necrosis or a rapidly progressive glomerulonephritis. The results of treatment of patients with an acute recoverable lesion

are simply stated. Either the patient survives or dies. In an evaluation of the overall results in the unit this simple assessment becomes meaningless. Subdivision of the patients into groups is essential if any proper analysis of treatment is to be made. Those who have died have been placed into one of three groups based on post-mortem pathological criteria: (1) recoverable acute lesions, (2) irrecoverable acute lesions, and (3) advanced chronic lesions.

Results of Treatment

Acute Recoverable Renal Failure

Details of the 45 patients in this group are set out in Tables I and II. In those patients with renal failure associated with jaundice due to a hepatic lesion (Table II) the prognosis is primarily dependent on the hepatic lesion, and in the great majority of them it is extremely poor. The separation of this group within that of acute recoverable renal failure is intended to emphasize this point and to avoid presenting an unnecessarily poor prognosis in the general group.

Of the 36 patients with acute recoverable renal failure without an associated hepatic lesion, 27 recovered from the renal failure. Ten suffered severe trauma with multiple injuries and one had severe extensive burns. Five of those with multiple injuries survived despite extreme degrees of trauma and periods of oliguria of 6, 20, 20, 16, and 71 days; dialysis was not performed in one, and 3, 2, 2, and 5 dialyses were performed in the other four. The extent of the trauma in the surviving patients (Cases 8/58, 11/58, 21/58, 18/59, and 23/59) is briefly set out in the case summaries, and Fig. 1 shows details of Case 11/58. Of the six patients

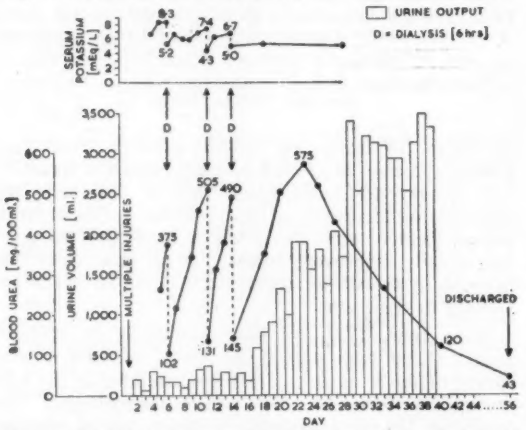

FIG. 1.—Case 11/58, man age 45. Typical chart of a patient with multiple injuries and acute renal failure. Note the necessity for early transfer and dialysis. (See case history.)

who died after severe trauma or burns, one (Case 32/58) with severe cerebral contusion and another (Case 22/59) with a fractured skull and cerebral damage died within a few hours of admission. Another patient (Case 35/59), with abdominal injuries and a fractured pelvis, died shortly after the commencement of dialysis, 16 hours after admission. The first patient (Case 1/57) to be treated with haemodialysis in the unit died the day after dialysis. The small girl (Case 1/59) with 65% burns died soon after the completion of a short dialysis on the day after admission. Patient 28/59 had sustained cerebral contusion and extensive trauma necessitating leg amputation; she died in the early diuretic phase during an episode of peripheral vascular failure not apparently related to any metabolic disturbance. The extent of trauma in those dying was not necessarily greater than in those surviving, although severe cerebral damage militated against recovery.

Of the six patients with acute renal failure related to pregnancy, five survived. The one patient (Case 5/58) who died during the early diuretic phase had had a post-partum haemorrhage. After an oliguric period of 12 days her urine volume had risen to 2.5 litres at the time of death, which was due to pulmonary embolism from infected thrombi in the large veins at the site of intravenous catheters.

In the third group of patients with miscellaneous causes for the renal failure, 17 out of 19 recovered from the renal failure. Two of these subsequently died from unrelated causes. Of the two patients dying before recovery of renal function occurred, one (Case 5/59) developed a further cerebral haemorrhage from an angioma, probably associated with the heparinization for dialysis, and the other (Case 36/59) died with severe post-operative abdominal sepsis.

Nine patients were admitted with renal failure associated with jaundice due to a hepatic lesion (Table II). Only two of these nine survived; of the seven who died, six came to necropsy, and all showed pathological changes in the kidneys consistent with a diagnosis of acute tubular necrosis. The hepatic lesions included hepatitis, either virus or leptospiral, suppurative cholangitis, and obstructive jaundice after operation on the bile passages. The prognosis in hepatic jaundice complicated by renal failure is extremely poor. The precise relationship of the jaundice or hepatic dysfunction to the onset of renal failure is obscure, although both in the terminal stages of hepatic failure and after operations on the bile passages in jaundiced patients hypotension with renal ischaemia may play an important part (Hecker and Sherlock, 1956; Lassen and Thomsen, 1958). It is possible that a high concentration of bile pigments in the serum potentiates the renal damage (Wartman *et al.*, 1950), and it may be that only those patients survive in whom the jaundice is rapidly lessening during the early stages of renal failure. This was, in fact, the case in two patients who survived (Cases 40/59 and 44/59), and fits in with previous personal experience and scattered reports in the literature.

In the only fatal case in which the jaundice was diminishing (Case 42/59) an early return of renal function had occurred when the patient died of a cerebral haemorrhage. In this case dialysis was performed on five occasions, and the patient had shown considerable improvement after an initial critically ill condition. Although the build-up of nitrogen retention was rapid, the main reason for the short intervals between dialyses was the belief that in the presence of combined hepatic and renal failure there is a rapid accumulation of toxic metabolites, in particular ammonia, other than those found with isolated renal failure (Webster and Gabuzda, 1959). Although it is impossible to deny that the cerebral haemorrhage in this exceedingly ill patient may have been related to the heparinization during dialysis, his striking improvement, with an early return of renal function, would seem convincing evidence that frequent dialyses are the right policy in combined hepatic and renal failure.

It is surprising and disappointing that dialysis removes relatively small quantities of bile pigment; the biggest

TABLE I.—*Patients with Acute Recoverable Renal Failure* (36 *patients*—27 *recovered from their renal failure*)

Case No.	Sex	Age	Renal Lesion	Associated Conditions	Maximum Blood Urea (mg./100 ml.)	Period of Oliguria (Days)	No. of Dialyses	Days in Renal Unit	Result
1/57	M	43	Acute tubular necrosis	Severe trauma; multiple fractures	400	7	1	3	Died
3/57	F	21	,, ,, ,,	Ante-partum haemorrhage	300	10	0	21	Recovered
4/57	F	27	,, ,, ,,	Septic abortion	570	21	3	75	,,
1/58	F	37	Ureteric obstruction	Hysterectomy (carcinoma of cervix). Cerebral angioma	280	8	0	3	Died (recovered from renal failure)
3/58	F	57	Acute tubular necrosis (single kidney)	Right staghorn calculus. Right nephrectomy	360	19	1	43	Recovered
4/58	M	15	Acute tubular necrosis	Acute dilatation of stomach. Gastrostomy. Hypotension	540	8	1	17	,,
5/58	F	20	,, ,, ,,	Post-partum haemorrhage. Terminal septicaemia with pulmonary embolus	480	12	1	10	Died
8/58	M	33	,, ,, ,,	Trauma. Multiple fractures. Diffuse pulmonary haemorrhage	430	6	0	49	Recovered
11/58	M	45	,, ,, ,,	Trauma. Multiple fractures	580	20	3	55	,,
19/58	M	23	,, ,, ,,	Carcinoma of stomach. Gastrectomy. Prolonged vomiting. Bowel perforation	540	13	1	37	Died (recovered from renal failure)
21/58	F	46	,, ,, ,,	Trauma. Multiple fractures	590	20	2	39	Recovered
22/58	M	26	,, ,, ,,	Acute alcoholism. Epilepsy. Right infantile hemiplegia	580	15	1	33	,,
23/58	M	35	,, ,, ,,	Peptic ulcer. 1951 gastrectomy. 1952 gastro-enterostomy. Prolonged vomiting	450	14	1	24	,,
25/58	F	35	,, ,, ,,	CO poisoning. Muscle necrosis. Neurological sequelae	540	20	2	82	,,
31/58	M	23	,, ,, ,,	Resection coarctation of aorta	380	14	1	30	,,
32/58	M	23	,, ,, ,,	Trauma. Cerebral contusion. Therapeutic hypothermia	360	8	0	Hours	Died
1/59	F	7	,, ,, ,,	Severe burns (65%)	360	Maintained urine volume	1	2	,,
3/59	F	23	Pyelonephritis	Complicating pregnancy—onset at 34 weeks of pregnancy with premature labour and stillborn infant 35 weeks. Staphylococcal enteritis	500	21	2	36	Recovered
5/59	M	16	Acute tubular necrosis	Cerebral angioma. Intracerebral bleeding	550	9	1	2	Died
8/59	M	19	Acute glomerulonephritis	Bronchopneumonia	320	9	0	64	Recovered
9/59	M	19	Renal vein thrombosis	—	160	10	0	75	,,
13/59	F	60	Acute tubular necrosis	Mitral stenosis. Pulmonary infarction	470	15	1	21	,,
15/59	F	23	,, ,, ,,	Concealed ante-partum haemorrhage after toxaemia of pregnancy. Foetal death *in utero*	410	20	1	32	,,
18/59	M	17	,, ,, ,,	Trauma. Multiple fractures	700	16	2	25	,,
20/59	M	27	,, ,, ,,	Dental abscess immediately preceding onset of renal symptoms	580	23	2	41	,,
21/59	M	21	Glomerulonephritis	—	256	10+	0	14	,,
22/59	M	35	Acute tubular necrosis	Trauma. Fractured skull	590	9	0	Hours	Died
23/59	M	54	Acute tubular necrosis and ? mild cortical necrosis	Trauma. Ruptured ileum. Amputation left leg, after thrombosis of femoral artery	600	71	5	134	Recovered
26/59	M	41	Acute tubular necrosis	Acute pancreatitis	380	12	0	18	,,
27/59	M	39	,, ,, ,,	Infected olecranon bursitis. Right nephrectomy. Secondary haemorrhage	520	52	4	76	,,
28/59	F	68	,, ,, ,,	Trauma. Subarachnoid haemorrhage. Multiple fractures. Right leg amputation	420	8	0	17	Died
30/59	M	68	,, ,, ,,	Salicylate poisoning. Bladder-neck obstruction. Prostatectomy	394	12	1	96	Recovered
31/59	F	20	,, ,, ,,	Septic abortion	550	24	1	31	,,
35/59	M	50	,, ,, ,,	Trauma. Pelvis fracture. Abdominal haematoma	400	5	1 (uncompleted)	2	Died
36/59	M	47	,, ,, ,,	Haematemesis and melaena. Gastro-enterostomy. Wound abscess. Further laparotomy	490	14	1	4	,,
41/59	F	44	,, ,, ,,	Pyloric stenosis. Mitral stenosis Gastro-enterostomy (carcinoma stomach)	470	12+	1	16	Recovered

TABLE II.—*Renal Failure in Patients with Jaundice* (9 *patients*—2 *recovered*)

Case No.	Sex	Age	Renal Lesion	Associated Conditions	Maximum Blood Urea (mg./100 ml.)	Period of Oliguria (Days)	No. of Dialyses	Days in Renal Unit	Result
29/58	M	73	Acute tubular necrosis	Obstructive jaundice. Cholecystectomy. Suppurative cholangitis	370	9	1	1	Died
30/58	M	51	,, ,, ,,	Resection gangrenous gut. Hepatitis	465	6	0	2	,,
7/59	M	40	,, ,, ,,	Hepatitis	390	8	1	6	,,
24/59	F	24	No post-mortem	Obstructive jaundice. Cholecystectomy. Intraperitoneal haematoma. Secondary removal of gall-stones in common bile-duct	450	13	1	6	,,
29/59	F	66	Acute tubular necrosis	Hepatitis. Cholecystectomy	470	24	4	16	,,
38/59	M	52	,, ,, ,,	Cholecystectomy. Obstructive jaundice. 2 exploratory laparotomies	450	15	2	13	,,
40/59	M	43	,, ,, ,,	Leptospirosis (Weil's)	560	6	1	19	Recovered
42/59	M	26	,, ,, ,,	,, ,, Cerebral haemorrhage	540	22	5	18	Died
44/59	M	49	,, ,, ,,	Cholangitis. Septicaemia (*E. coli*)	480	10	1	35	Recovered

fall in the serum bilirubin with a six-hour dialysis was from 51 to 38 mg./100 ml., when the blood urea fell from 500 to 190 mg./100 ml. (Case 42/59). That this is not due to release of bile pigment from the tissues maintaining the serum level is apparent from the very low concentration of bile pigment in the dialysing fluid. Nevertheless, repeated dialyses will also help to reduce the serum bilirubin level and possibly allow renal function to recover more rapidly.

Acute Renal Failure with Irrecoverable Renal Lesions

Of the 12 patients in this group, one had extensive symmetrical bilateral cortical necrosis; this was a woman of 25 (Case 16/59) who developed renal failure after concealed accidental haemorrhage at full term in her fifth pregnancy. A live child was delivered after rupture of the membranes, but it died in 24 hours. The patient was admitted to the unit on the eighth day of renal failure and was dialysed on one occasion (tenth day). She was subsequently managed conservatively, with the addition of norethandrolone ("nilevar"), but the urine volume never exceeded 300 ml. in 24 hours, and she died on the forty-sixth day of renal failure.

At necropsy 11 patients, all men, aged from 18 to 52 years, showed the pathological changes compatible with the diagnosis of "subacute glomerulonephritis." One man of 23 came to necropsy with very unusual arterial lesions in the kidneys resembling those seen in scleroderma. Full details of this patient and those with "subacute glomerulonephritis" will be published elsewhere.

A boy of 11 (Case 5/57) was admitted in acute renal failure associated with gross purpuric eruptions and abdominal pain. He was dialysed on one occasion, but died, still in severe renal failure, as a direct result of the rupture of the bowel. Necropsy showed widespread lesions typical of periarteritis nodosa. A woman of 59 was admitted with severe purpura and a blood urea of 700 mg./100 ml.; she died before dialysis was started. At necropsy the kidney showed diffuse necrotic lesions in the glomeruli. The adrenal glands were largely destroyed by haemorrhage. Thirteen dialyses were performed on 11 of these patients.

Renal Failure with Advanced Chronic Renal Lesions

Seventeen patients were admitted in renal failure and proved eventually to have chronic renal lesions. Of the 17, 13 died of renal failure, either while in the renal unit or shortly after transfer to their parent hospital. Nine of these 17 patients had chronic glomerular nephritis, five had long-standing post-renal obstruction; and of the other three, one had polycystic kidneys, one chronic pyelonephritis without obstruction, and one renal amyloidosis complicating chronic osteomyelitis (present for 35 years).

Of the four patients who survived, three had post-renal obstruction (severe hydronephrosis with one kidney, chronic prostatic obstruction, and colonic transplantation of both ureters), and all three greatly improved while in the unit, two of them each being dialysed once. The other was one of the patients with a chronic lesion and ankylosing spondylitis.

Of the 17 patients, 11 were dialysed on 15 occasions.

Poisonings

We have seen four patients (one in renal failure) with drug poisoning, three due to barbiturates and one due to glutethimide (α-phenyl-α-ethylglutarimide; "doriden"). One patient with barbiturate poisoning was not dialysed as his level of consciousness was rising and the day after admission he regained consciousness. The patient with the glutethimide poisoning came to us too late; he died within three hours of admission and before we were able to start dialysis, which would have been expected to remove a considerable amount of the drug.

The other two with barbiturate poisoning were dialysed in their own hospitals. Case 24/58 has been described (Honey and Jackson, 1959). The second patient, a woman of 54 (Case 39/59), had taken a large dose of phenobarbitone and later developed a short period of renal failure. She was dialysed for eight hours in her own hospital with a successful outcome (Fig. 2).

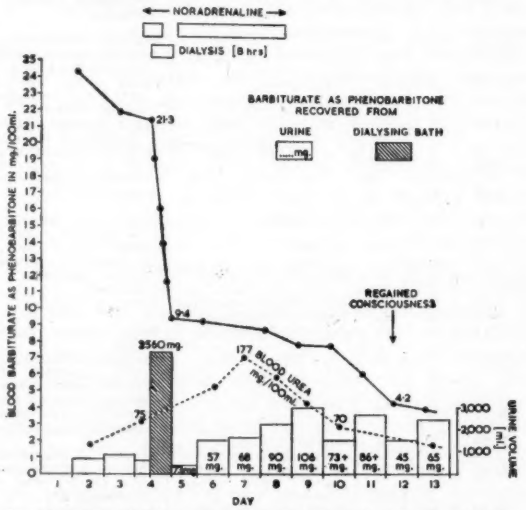

FIG. 2.—Case 39/59, woman age 54. Phenobarbitone poisoning. Barbiturate removed:—Bath: dialysis—8 hours=2.560 g.; Urine: 17.4 litres in 8½ days=0.663 g. (Patient under the care of Dr. Clifford Parsons. Barbiturate estimations made by the biochemistry staff, General Hospital, Birmingham, where dialysis was performed.)

The artificial kidney may come to play a more active part in the treatment of severe barbiturate poisoning with or without the presence of renal failure, particularly in the large cities, where many cases of such poisoning occur.

The removal of barbiturate from a patient by an artificial kidney will depend on the degree of binding of the drug with the protein molecule. The longer-acting the barbiturate the better is the result of haemodialysis (Table III). Even mild renal failure may be an imperative indication for dialysis if intoxication is due to a dialysable compound.

TABLE III.—*Barbiturate Poisoning. Expected Results from Haemodialysis*

Barbiturate	Proprietary Name	Action	Blood Level to Produce Unconsciousness*	Expected Results from Haemodialysis
Barbitone ..	Medinal	Long	5–9	Very good
Phenobarbitone ..	Luminal	,,	5–9	,, ,,
Butobarbitone ..	Soneryl	Intermediate	2–4	Moderate
Amylobarbitone ..	Amytal	,,	2–4	,,
Pentobarbitone ..	Nembutal	Short	1–2	Poor
Quinalbarbitone ..	Seconal	,,	1–2	,,

* mg./100 ml. expressed as the acid form of the barbiturate. (From *Micro-analysis in Medical Biochemistry*, 3rd ed., 1956, King, E. J., and Wootton, I. D. P. Churchill, London.)

Miscellaneous

Two patients are not included in the above groups. One had hypokalaemic alkalosis and was not dialysed but recovered. The other, aged 72, had myocardial ischaemia, a hypernephroma of one kidney, with obstruction to the other by glands causing prolonged anuria: he was dialysed twice but died.

Management of Patients

Conservative Treatment

The successful management of acute renal failure depends largely on early diagnosis. The sooner proper metabolic care of the patient is begun the more likely is the course of the illness to be undramatic and conservative management, without recourse to dialysis, allow the recovery of renal function. Although acute renal failure may occur without oliguria (Sevitt, 1959), the metabolic disturbances are usually less and the failure to recognize the presence of the renal functional damage is not so dangerous to the patient as when oliguria occurs. The term "anuria" is often used to describe these cases, with the implication that they are only in renal failure when anuric. In fact, the majority have oliguria, but if anuria is present the most likely cause is a post-renal obstruction. An arbitrary 24-hour-urine volume of 760 ml. as a definition of oliguria has been suggested (Joekes *et al.*, 1957), as at this rate of urine flow (0.5 ml./min.) well-marked urine concentrations should be expected, with a specific gravity of 1020 or more or an osmolarity in excess of 1,000 ml. osm./l. in the presence of normal renal function. If with such a urine volume the specific gravity is below 1016, renal functional impairment must be assumed. If doubt exists about the presence of renal damage despite a good urine volume, the urinary urea concentration should exceed 2 g./100 ml., irrespective of the urine volume if the blood urea is over 100 mg./100 ml. (Taylor, 1957).

It cannot be too strongly emphasized that observations on the urine will facilitate an early diagnosis of acute renal failure, whilst isolated observations on the blood chemistry cannot differentiate between primary metabolic disturbances and renal failure.

Once the presence of acute renal failure is established simple metabolic control should be started immediately. Total fluid intake must be strictly controlled, and it is now fully established that the patient should be rationed to an electrolyte-free carbohydrate solution with no fat, whenever possible by mouth without intubation. While the optimal total calorie intake is still uncertain it should not fall below 400–600 calories for prolonged periods. Management varies, depending on the phase of acute tubular necrosis.

This aspect has been adequately discussed by many authorities, including Parsons and McCracken (1959). It is essential that the intake of fluid is restricted to not more than 600 ml. daily to cover insensible loss. The aim should be to maintain a daily loss of weight of about 300 g. during the oliguric phase. Lactose by mouth has been found to be tolerated better than glucose. Apart from patients with severe trauma the vast majority tolerate oral feeding, thus avoiding unnecessary intravenous therapy. Antibiotics are not now prescribed as a routine but only when indicated.

When the oral route is not possible (45 g. daily) large doses of rectal "resonium-A" up to 200 g. a day* have helped significantly to reduce the rate of rise of serum potassium.

With the onset of the diuretic, or recovery, phase (usually 1 litre or more urine output in 24 hours) great care is required in estimating electrolyte losses in the urine, particularly potassium and sodium, because supplements may be required.

Haemodialysis

Indications.—(1) Overhydration, particularly in the presence of pulmonary oedema, because of the constant risk of sudden collapse, with hypotension. (2) Hyperkalaemia of 7mEq/l. or more, with electrocardiographic changes. (3) Acidosis of 12 mEq/l. or less which cannot be corrected. (4) Clinical deterioration is the single most important indication for dialysis. Patients should not be allowed to develop a state of established persistent vomiting, drowsiness, or twitching, whatever their biochemistry, because their subsequent management becomes more difficult. In patients with trauma our experience has shown it is essential to dialyse early owing to increased katabolism. (5) Poisoning by drugs, such as barbiturates and salicylates, associated with renal failure.

If surgery is essential in treating the primary condition causing the renal failure, then often a planned dialysis 24 hours before the operation is indicated, recognizing that a further dialysis perhaps 24 to 48 hours after operation may be necessary. There are no contra-indications to dialysis with this apparatus.

Technique.—The Kolff twin-coil artificial kidney (Travenol Lab. Inc.) has a fixed capacity of about 1,000 ml. Immediately before dialysis begins the circuit is tensed by the addition of small amounts of blood to a pressure of 200 mm. Hg. The flow-rate can be varied, but is usually maintained at about 350 to 450 ml./min. The pressure in the circuit can also be varied considerably; if ultrafiltration is not required to any extent the pressure is reduced accordingly. Artery-to-vein connexion with the "kidney" is used in most patients. Tapered polyvinyl chloride catheters (Portex) with a side-arm for sampling are used. They are presterilized and kept in separate nylon envelopes. The whole procedure of catheter insertion and dialysis is now performed by one medical officer and one sister. Modifications have been made to the "kidney" and are described elsewhere (Brennand and Bunker, 1960). In the case of cerebral injuries and patients with jaundice, regional heparinization as recommended by Anderson and Kolff (1959) may reduce haemorrhagic complications due to dialysis.

Dialysing Fluid.—The bathwater or dialysing fluid is that commonly in use containing potassium, sodium, chloride, and bicarbonate in concentrations equal to those found in normal plasma with 0.4% glucose. A high serum potassium is reduced to a normal level by omitting potassium from the bath for the first one or two hours. The bath is changed every two hours.

Results of Dialysis

Table IV shows an analysis of the range of the biochemical results and fall in blood urea for 62 dialyses of six hours' duration. Hyperkalaemia is corrected

**Preparation of resonium-A for rectal administration* (100 g. dose).—Resonium-A, 100 g.; aqua dist., 150 ml.; "promulsin gel" (5% solution), 50 ml. Dilute the promulsin gel with the water and incorporate resonium-A in a mortar. Transfer to an M.R.C. 500-ml. intravenous-drip bottle.

Promulsin gel.—Promulsin powder, 50 g., aqua chlorof., ad 1,000 ml.

Note: 50 ml. of mucilage of tragacanth may be substituted for promulsin gel.

easily, also sodium and chloride concentrations in most patients. In seven dialyses (six patients) the serum sodium at the end was over 148 mEq/l.; however, four of these recovered. (The other two eventually died with hepatic failure and septicaemia.) Acidosis was corrected satisfactorily in most patients. At the end of dialysis a serum bicarbonate of 22 mEq/l. or less was present on five occasions, in three patients with chronic renal lesions and in two with colonic transplantation of the ureters. In the latter, serum bicarbonate of 6 and 8 mEq/l. were corrected to 21 and 22 mEq/l. respectively.

TABLE IV.—*Biochemical Results of Dialysis (Six Hours)*

No. of Dialyses:	62	60	60	60	62
	Blood Urea (mg./100 ml.)	Serum Sodium (mEq/l.)	Serum Chloride (mEq/l.)	Serum Bicarbonate (mEq/l.)	Serum Potassium (mEq/l.)
Beginning of dialysis ..	700–116	161–112	124–70	32–6	9·2–2·1
Mean	467	134	92	17·4	5·9
Standard deviation ..	±95·5	±9·8	±9·4	±4·6	±1·4
End of dialysis	264–71	162–120	112–88	31–19	6·2–2·8
Mean	144	140	101	25·7	4·2
Standard deviation ..	±45·9	±8	±5·8	±2·8	±0·7

With regard to the fall of blood urea throughout dialysis, it is recognized that the urea clearance in the Kolff twin-coil is not as great as that in the Skeggs–Leonards or rotating-drum machines (Anthonisen *et al.*, 1956; Parsons and McCracken, 1958). However, this fact has not necessitated, in this unit, more frequent dialyses in any individual patient or prejudiced recovery. Of our 57 patients dialysed, 73% had one or two dialyses only.

The clinical state of the majority of patients has improved during or 24 hours after dialysis. Only a few patients have shown clinical deterioration during dialysis, associated with a hypotension which has been usually corrected with a small blood transfusion (200–300 ml.) into the extracorporeal circulation. Hypertension has not been a feature of dialysis, apart from two patients with malignant hypertension. Pulmonary oedema has been improved considerably. This change can be demonstrated radiologically. Where accurate weights before and after dialysis have been obtained, all patients showed a fall in weight, with a range of 0.6 to 4.5 kg., with fluid replacement in some patients. The loss of weight reflects removal of water due to ultrafiltration.

Cases of Extensive Trauma which Recovered

Case 8/58.—Late on April 16, 1958, a man aged 33 sustained the following injuries in a car accident: five fractured ribs, haemothorax with generalized alveolar haemorrhages, extensive bruising to the abdominal contents with a ruptured spleen, fractured pelvis, right femur, right and left tibiae and fibulae, and left elbow. The next morning he underwent a laparotomy and splenectomy, and 450 ml. of blood was withdrawn from the left chest. Later the same day a tracheostomy was performed. Within 24 hours of the accident he was given 19 pints (10.8 litres) of blood. Immediately after the accident he was oliguric, with a rapidly increasing uraemia. On the third day he was transferred to this unit, at which time the blood urea was 259 mg./100 ml. and the 24-hour-urine volume 248 ml. He was placed in an oxygen tent for three days. On the fifth day of renal failure he produced 1,500 ml. of urine in 24 hours and subsequently made a full recovery without dialysis because of the short oliguric phase.

Case 11/58.—A man aged 45 fell 80 ft. (24.4 m.) while cleaning windows on April 25, 1958. During his fall he ricocheted on his back off some telephone wires. His injuries were: concussion, considerable bruising of the back with extensive comminuted fractures of right scapula, pelvis, and right acetabulum with displacement, and fractures of four ribs and of both femoral necks. He was transferred to this unit on the fifth day; details are shown in Fig. 1. He made a good recovery, returning to work but cleaning ground-floor windows only.

Case 21/58.—A woman aged 46 was injured in a car accident on August 3, 1958. She was concussed and sustained a fractured pelvis, right ankle, and humerus; the left diaphragm was perforated, and the stomach and spleen had herniated into the thorax. The same day she was operated on to repair the diaphragm. Over the next eight days the volume of urine ranged between 60 and 450 ml./24 hours and the blood urea rose to 400 mg./100 ml. On the ninth day she was transferred to this unit. During the next six days she was dialysed twice; on the 21st day after the accident she produced 1,500 ml. of urine and proceeded to an uneventful recovery.

Case 18/59.—On May 25, 1959, a youth of 17 was involved in a motor-cycle accident. He sustained the following injuries: severe concussion, numerous contusions, a fractured vertebra, fractured pelvis with right protrusio acetabuli and subluxation of the right sacro-iliac joint, compound comminuted fracture of the right femur, and a fracture of the right tibia. There was absent circulation to the right foot. The same day he underwent an operation to decompress a haematoma of the right calf and insert a Steinmann pin. By May 27 a definite line of demarcation had appeared across the right foot, with incipient gangrene distally. He had remained oliguric since the accident (0–350 ml./24 hours). On June 1, when admitted to Halton, he was disorientated, had produced only 200 ml. of urine in 24 hours, the blood urea was 550 mg./100 ml., and the serum potassium 6 mEq/l. During the next five days he was dialysed twice; on the 17th day after the accident he began a diuresis. The right foot improved throughout the oliguric phase, and eventually complete circulation was restored. During most of his illness his management was complicated by severe mental disorientation resulting from his post-concussional state. He made an uneventful recovery; by the 28th day the blood urea was 38 mg./100 ml.

Case 23/59.—At 11 a.m. on June 16, 1959, a man aged 54 was kicked in the left groin by a horse. By midnight a large haematoma had developed in the left lower abdominal wall and the left leg was numb, painful, and pulseless. A block at the left ilio-femoral arterial junction was demonstrated by aortogram. Laparotomy revealed gross peritonitis and a ruptured ileum from a necrotic left inguinal hernial sac. Resection of the bowel and artery was performed, the operation lasting nine hours. The immediate post-operative progress was favourable, but it was doubtful if full circulation had returned to the leg. During the eight days after the accident the volume of urine rose gradually from nil to 950 ml./24 hours, the blood urea to 510 mg./100 ml., and the serum potassium to 6.6 mEq/l. At this stage he was transferred to Halton; on arrival it was apparent that the left lower leg was not viable. Haemodialysis was performed on the 10th day and a left mid-thigh amputation on the day after. Post-operatively an extremely rapid rise in uraemia occurred, necessitating a further dialysis on the 12th day. He proceeded to a prolonged oliguric phase lasting 71 days from the day of injury; during this period he required five dialyses. On the 134th day he was referred back to his parent hospital with a urine volume of 4 litres and blood urea of 190 mg./100 ml. At the time of writing he had returned home and was in the early stages of rehabilitation with an artificial limb.

Discussion

Any analysis of the results of treatment of acute recoverable renal failure on a comparative basis is difficult, if not impossible, as underlying or complicating conditions, rather than the renal failure, may determine

the outcome. Some assessment of the results is, however, essential, as the main justification for specialized units treating renal failure must be a higher rate of success than in non-specialized centres. As stated in the introduction, all patients admitted to the unit have been placed into one of three categories of renal disease: (1) recoverable acute lesions, (2) irrecoverable acute lesions, and (3) advanced chronic lesions. It is primarily the results in the first group that must be considered.

A total of 45 patients with acute recoverable renal lesions are included in the present series. Nine of these cases occurred in association with hepatic lesions and have been separately presented, as it is argued that the prognosis depends entirely on the hepatic lesion. Only the two patients with diminishing jaundice recovered, the seven other patients dying with severe hepatic insufficiency. Of the other 36 patients with acute recoverable renal failure, 27 recovered from the renal failure. The background to the renal failure in these cases had a very wide spectrum, including extensive trauma. Of 10 patients with severe trauma, five survived; the severity and extent of the trauma was not necessarily less in the surviving patients, although cerebral damage was of grave prognostic importance, in keeping with the results reported by Taylor (1957), only 5 out of 31 patients surviving where acute renal failure complicated head injuries.

Lucké (1946) reviewed some 600 published cases of acute renal failure, and estimated the overall mortality as in excess of 90%. It was not until after 1946 that treatment based on simple metabolic lines during the period of renal failure profoundly altered the desperate prognosis of this condition.

Clinical application of haemodialysis has been effected by Kolff and Berk (1943), but not until the fundamental principles of metabolic care were applied in the management of the patients and further advances in dialysing technique had occurred could haemodialysis convincingly be accepted as altering the overall prognosis.

Hamburger (1957) reported 203 cases of acute renal failure treated routinely by haemodialysis; the mortality figure was only 9%, but many mild episodes of renal failure were included among the cases. The earliest report in this country of the use of haemodialysis (Bywaters and Joekes, 1948) described 12 cases, of which only four had reversible lesions, two of these patients surviving. Shackman and Milne (1957) reported 30 cases with renal failure, 14 of which were treated with dialysis. None of the latter patients survived, but in 10 of them conditions other than renal failure accounted for death or an irreversible renal lesion was present. Of the 16 patients treated conservatively, 12 survived. Brief mention is made of subsequent results (Shackman, 1959), in which 26 patients with recoverable renal lesions were dialysed on one or more occasions, of these 15 died. Parsons and McCracken (1959) reported 63 cases of acute reversible renal failure; 7 of 18 (39%) patients treated conservatively died, but six of these died shortly after admission before dialysis could be attempted, and 17 (38%) of 45 patients who were dialysed died. Four of the latter group had renal failure complicating hepatic lesions, and three of them died. In the present series, patients with acute reversible renal lesions, excluding those with primary hepatic disease, had a survival rate of 75%, there being little difference whether conservative management alone or dialysis was used (Table V). Patients with the more prolonged renal failure or other complications were dialysed in the present series, and the very similar survival rate in those who were dialysed as in those who were not must be accepted as evidence for an improved rate of survival due to dialysis.

TABLE V.—*Results of Treatment of Patients in the Different Groups*

Group		Not Dialysed	Dialysed	Recovered from Renal Failure
1	Acute recoverable renal failure	10	—	6
		—	26	21
	Renal failure with jaundice	1	—	0
		—	8	2
2	Acute irrecoverable renal lesions	1	—	0
		—	11	0
3	Chronic renal lesions	6	—	Improved 2
		—	11	2

Taylor (1957) reported 31 cases of renal failure complicating head injury. Conservative management only was used, and of the 31 patients only five survived. Whether haemodialysis could improve these results in such a group can be answered only on the basis of experience. With the technique of regional heparinization, where there should be no prolongation of the clotting-time in the patient's body, haemodialysis would then not entail the added danger of cerebral bleeding. The experience in Korea in 1950, with renal failure complicating severe trauma (Smith *et al.*, 1955), leaves little doubt that haemodialysis greatly improves the survival rate. In the present series the survival of five patients with extensive trauma, the case histories of which are recorded above, is striking, and it must be very doubtful whether in those with longer-lasting oliguria survival would have been possible without haemodialysis.

If it is accepted that some form of dialysis must be available for any patient with acute renal failure should the necessity occur, a further question arises of the type of dialysis that should be employed. Peritoneal dialysis has the advantage that only very simple equipment is required, but 36 hours' dialysis effects the same metabolic exchanges that occur with six hours' haemodialysis or less with an artificial kidney. As constant supervision of the patient is required throughout the peritoneal dialysis and considerable discomfort to the patient is at times caused, it is doubtful whether peritoneal dialysis could be accepted as the method of choice in patients in whom repeated dialysis at relatively short intervals may be required. Exchange transfusion is fundamentally obtaining the same effect as haemodialysis, but the large quantities of blood make this impracticable, quite apart from the possible disadvantages of introducing the necessary amount of blood from other individuals. Gastro-intestinal dialysis has a relatively poor effect on the biochemical abnormalities except in removing potassium; and this, together with the marked discomfort to the patient, suggests that the method is unsuitable.

The large number of reports of haemodialysis using different types of apparatus can leave no doubt that, used by an expert team, this is a safe and often essential procedure. The type of apparatus used is certainly less important than the experience of the team. It is possible to place the different types of artificial kidney into two main groups: (1) those with a large potential capacity in the dialysing membranes, which is, however, only partly filled (the Kolff rotating drum); and (2) those in

which the potential capacity in the dialysing membrane is fully filled (Alwall kidney, Kolff twin-coil kidney, Skeggs–Leonards kidney, and others). With both the Skeggs–Leonards and the Kolff twin-coil kidney there is reasonable certainty that the full capacity of the dialysing membrane can be filled before connecting the patient; this is possibly less easy in the Alwall kidney, where the prevention of distension of the dialysing membrane tube beyond the original filling is less certain.

Only in kidneys in the second group, with a restricted capacity in the dialysing membrane, can a positive pressure be built up with the gradient from blood to dialysing fluid, thus enabling water to be lost by ultrafiltration. Although this may not be of great importance in many cases that are dialysed, there is little doubt that it is extremely important to be able, with certainty, to prevent take-up of water from the dialysing fluid. Shackman and Milne (1957), using the rotating-drum type of artificial kidney, found that there was a take-up of water by the patient which they assessed at approximately 500 to 600 ml., and in several of their patients the occurrence of pulmonary oedema after dialysis apparently contributed to the fatal outcome. Parsons and McCracken (1959), while appreciating the inability of a rotating-drum type of kidney such as they used in their unit to remove water from the patient, suggested that the total clearance obtained with this type outweighed the disadvantages. We have no doubt that some form of artificial kidney of limited capacity is the apparatus of choice and is essential in treating overhydrated patients.

In some countries the number of units with facilities for haemodialysis has far exceeded that in this country, where in the last few years only three units specifically handling acute renal failure have been in existence. More recently a considerable number of artificial kidneys have been bought or constructed, and some of these are intended for use in units accepting any patients in renal failure. The figures of survival rates in specialized units such as have been presented in the present paper, taken in conjunction with the impossibility of predicting the length of the oliguric renal failure, would seem to lead to two conclusions: (1) all patients with more than a transient acute renal failure should be transferred to specialized units; and (2) the establishment of specialized units with facilities for haemodialysis should be on a planned regional basis, taking into consideration population densities.

Summary

A survey is made of the results of treatment of 80 patients in a unit with haemodialysis facilities during a two-year period. 78 patients were admitted and 88 dialyses performed on 57 of them. A further two patients were dialysed successfully once each in their own hospitals.

Acute recoverable renal failure occurred in 36 patients and 27 recovered from their renal failure. Nine further patients in this group, but with associated hepatic lesions, two of whom recovered, are discussed separately as the prognosis is thought to depend on the hepatic lesion. 29 cases of acute irrecoverable renal failure and chronic renal lesions are described and only four improved in these two categories. The use of the artificial kidney for barbiturate poisoning is discussed.

Emphasis is placed on early diagnosis of renal failure by observations on the urine rather than isolated estimation of the blood chemistry, and treatment is discussed.

The clinical state of the patient is the single most important indication for dialysis; other factors are marked hyperkalaemia of 7 mEq/l. or more, a severe acidosis of 12 mEq/l. or less, and gross overhydration. A description is given of the technique and results of dialysis.

The results of the present and other series are discussed and two conclusions are drawn: (1) all patients with more than a transient acute renal failure should be transferred to specialized units; and (2) the establishment of specialized units with haemodialysis facilities should be on a planned basis, taking into consideration population densities.

Case histories are given of five patients who recovered from extensive trauma.

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At a recent meeting of the Institute of Actuaries, Mr. J. S. THOMPSON, Secretary Treasurer of the Hospital Service Plan of New Jersey, U.S.A., presented a memoir on "Insurance against Costs of Hospital and Medical Services in the United States ('Blue Cross' and 'Blue Shield')." The memoir outlined the present organization and scope of the two services, and their very rapid growth since the war. The author envisaged a continuing growth, with greater refinements of underwriting techniques, unless costs increased so far and fast that "the insuring public find the rates intolerable and demand that the whole health service enterprise be taken over by the Government."

ALLEVIATION OF INTRACTABLE PAIN*

BY

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The past five years have seen the development of a new and more positive approach to pain to which the adjective "intractable" is in consequence becoming less applicable, although this description is still true of many cases of incurable cancer and non-malignant diseases, such as arthritis, which cause so much distress to the aged.

Much of the renewed interest in this condition has perhaps been due to the development of new analgesic drugs and tranquillizers that continue to appear in increasing volume, and to the work of Maher (1955, 1957), Nathan and Scott (1958), and Brown (1958) on intrathecal phenol.

No consideration of the problem of pain is possible without the appreciation that this is an intensely personal symptom and that pain thresholds vary widely in individuals. Congenital factors may play a part here, although, as Russell (1959) points out, this does not materially affect the problem except in so far as emotional factors may lower thresholds and complicate the pattern, pushing it further into the field of psychotherapy.

It is natural that the challenge of intractable pain should be accepted by anaesthetists, for they are well equipped to make a significant contribution to its treatment, both by virtue of a wide knowledge of modern analgesic drugs and by their experience of the approach to the subarachnoid space, which they have gained from the practice of spinal analgesia.

Analgesic Drugs

The use of pain-killing drugs has for centuries past been the front line of attack against the problem of pain. Because of their ease of administration and undeniable reliability, it is certain that they will continue to occupy this position. Morphine and its derivatives have long held pride of place here—so much so that they come to mind almost reflexly when one is faced with the treatment of these patients. Nevertheless, morphine has many undesirable side-effects, of which nausea, vomiting, constipation, and the clouding of mental processes are well known. At times the hypnotic effect of morphine is highly desirable, but probably mostly in the terminal stages of pain from malignant disease. Perhaps far too many patients are submitted too early to the merciful but despairing relief afforded by morphine, and the last months of life are spent in disorientation and uselessness, which is profoundly disturbing to their family and friends.

In the earlier stages of pain for which there is no medical or surgical cure, much can be done by the judicious administration of mild analgesic drugs; of these, tab. codein. co. is representative, and its long-continued use does not bring unwanted side-effects in its train.

In recent years there has been a considerable increase in the physician's armamentarium whereby he may control the more severe pain without recourse to his old ally, morphine. Many of these drugs are specific analgesics and are almost without hypnotic action. Under their influence patients may be relieved of their pain while fully able to work or deal with business affairs. Among those drugs which we might call the potent analgesics the following have shown considerable promise in the control of intractable pain: oxycodone pectinate, dihydrocodeine bitartrate, levorphanol tartrate, methadone hydrochloride, and dextromoramide.

Oxycodone Pectinate.—This compound consists of dihydrohydroxycodeinone combined with the pectin macro-molecule. The active alkaloid is released slowly in the body and when given intramuscularly in doses of 10–20 mg. its duration of action may last from 8 to 14 hours. Belam (1957), reporting on the use of this drug in 100 patients, did not find any sedative action, but confirmed its long-acting properties. I have administered this preparation in doses of 10–15 mg. during operations where a painful convalescence can be expected—for example, haemorrhoidectomy—and have been impressed with the degree and duration of the analgesic effect. In intractable pain controlled by morphine it can adequately replace the latter drug, although dosage may have to be initially as high as 30 mg. six- or eight-hourly. It has recently become available in 30-mg. suppositories and can therefore be self-administered by ambulant patients.

Dihydrocodeine Tartrate.—Gravenstein *et al.* (1956) reported this drug to be almost as effective as morphine with fewer side-effects. It is active when administered orally (30–60 mg.) or parenterally (30–50 mg.) and has no hypnotic or sedative properties.

Levorphanol Tartrate.—This drug was synthesized in 1949. Of two isomers, the dextro-isomer has a selective action on the cough centre. The laevo-isomer has a powerful analgesic action with few side-effects. It is reliable when taken by mouth in tablets of 1.5 mg., and up to three may be given to patients with severe pain. It is available in ampoules of 2 mg. for parenteral administration, and this should produce an effect for six to eight hours.

Methadone Hydrochloride.—This drug probably acts directly on the thalamus and, unlike morphine, does not cause depression of the higher centres. It is about equipotent with morphine in analgesic action and has a depressant action on the cough centre.

Dextromoramide.—This new and very potent analgesic is 7 to 18 times as powerful as morphine. It is one of the very few which are equally as effective whether administered by the oral or the parenteral route, and its therapeutic effect is very rapid. Duration of action depends on dosage, but averages four hours when a normal dose of 5–10 mg. is taken orally. Intravenously, 1–2 mg. produces effects which are observed almost immediately, and potentiation of other hypnotic drugs, concurrently administered, may be marked. Nausea, vomiting, and drowsiness are occasionally seen, but infrequently compared with morphine, and constipation has not been observed.

Addiction to Analgesic Drugs

It must be assumed that all the potent analgesics are capable of giving rise to addiction. Nevertheless, I have the very strong impression that analgesic drugs which have little or no hypnotic properties are very slow to

*Read in the Section of Anaesthetics at the Annual Meeting of the British Medical Association, Torquay, 1960.

produce addiction when compared with drugs which have this action in marked degree.

Although pain can often be adequately controlled by the use of analgesic drugs, prolonged administration often tends to produce depression of mental activity, and much benefit can be derived by the use of amphetamine or methyl phenidate hydrochloride to elevate mood. The tranquillizing action of the phenothiazine group can also be useful here, although the hypnotic action of analgesics, even if minimal, is often thus potentiated, and care is needed in balancing the dosage accordingly. Prochlorperazine was found by Bowen (1959) to be superior to chlorpromazine in controlling nausea and vomiting while showing only very weak potentiating properties.

Nerve Conduction Blockade

Apart from treatment by drugs, pain can be abolished by blocking the pathways by which pain reaches the central nervous system. The detailed consideration of surgical operations for the relief of severe pain are out of place here, belonging as they do within the sphere of neurosurgery. Nevertheless, they illustrate very well the degree of selectivity, in regard to pain fibres, which must be the basis of all attempts to combat pain, and they are therefore worthy of brief mention.

Interruption of pain conductivity can be brought about by (1) division of peripheral nerves, (2) section of posterior roots (post-rhizotomy), and (3) cordotomy, or diversion of tracts within the cord itself.

Most peripheral nerves contain both motor and sensory fibres and can regenerate after division. Clearly, therefore, the first of these procedures must be classified as crude and undesirable. At posterior root level, however, the afferent pathways may be cut without influencing motor function, but the loss of proprioceptive sensation and touch tends to trophic changes and may render a limb useless and a burden to its owner. The operation of cordotomy is a much more refined approach, directed as it is to the division of specific tracts conducting pain and temperature after dissociation within the cord, and leads to no more unpleasant sensations than mild paraesthesiae.

Technique

The technique, first described by Maher (1955), attempts to achieve "selective chemical rhizotomy" by the intrathecal injection of phenol in heavy conveying solutions and is of considerable interest, especially in the control of intractable pain in malignant disease.

This procedure may require some degree of mental reorientation on the part of anaesthetists, conditioned as they are by the necessity, heretofore, of excluding substances such as phenol from gaining access to the C.S.F. However, the corrosive action of phenol does not appear in the anhydrous state, and, whilst it is soluble in glycerin and ethyl iodophenylundecylate ("myodil"), it is rapidly absorbed by nervous tissue when brought into contact with nerve roots and ganglia in this state. This solution possesses, in addition, self-sterilizing properties, although it is usual to prepare fresh solutions sterilized by dry heat. Dogliotti (1931) used the intrathecal route to administer alcohol, in an attempt to interrupt pain-conduction in nerve roots without loss of sensory or motor function. In the C.S.F., alcohol is rapidly diluted before it damages the more myelinated motor roots, but not before producing a degree of damage to the fibres conducting pain. Accurate positioning of drugs injected below the arachnoid is essential, and alcohol, being exceedingly hypobaric, is not always easy to control.

A 5% solution of phenol in glycerin is heavier than C.S.F. and easier to position within the spinal canal. Moreover, it is not so susceptible to minor inaccuracies of spinal tilt. A solution of this strength will affect permanently the small pain fibres or cells of the posterior root ganglion without producing unwanted neurological sequelae.

Intrathecal phenol is especially valuable in severe pain from malignant deposits arising from primary growths of the leg—for example, sarcoma—or pelvis. Subarachnoid puncture is easier below D 12 and within the lumbar stretch, and there is no danger here of cord damage. With the use of a downward slope towards the sacrum, the solution can be made to run over the affected roots while the patient lies on the painful side. 1 ml. of solution is usually sufficient to influence four or five roots, and repeated injections can be given to cover all affected parts. Relief from pain is obtained within a few minutes if positioning has been accurate, and failures have been ascribed to the invasion of the posterior root ganglion by malignant cells and consequent sheltering of the nerve elements (Maher, 1957). Unilateral attack is less likely to cause bladder disturbances, which, however, are usually transitory and manifest by retention or slight hypotonia for 24 hours. Pre-existing bladder dysfunction, however, may be rendered permanently worse if the lower sacral roots are involved in the injection.

In the cervical region rather better results have been obtained by subdural than by subarachnoid injections of phenol in myodil (Maher, 1959, personal communication). The approach to the cervical subarachnoid space has been described as easily performed, although this has not been so easy in my own limited experience. Pressure of C.S.F. in this region, with a patient in the sitting position, is low, and, using a needle of 21 gauge, which is desirable, considerable patience on the part of the operator (and patient) is necessary to be sure the subarachnoid space has been reached. If the needle-point is carefully withdrawn until C.S.F. just ceases to flow, injection of 1 to 1.5 ml. may be made subdurally to affect cervical roots in brachial pain and, when myodil is the solvent, radiological confirmation of correct positioning may be obtained.

If injection is made during the withdrawal of the needle-point rather than at the position of maximal advance the extensive damage which would result from injection of phenol solutions into the cord substance is obviated, whilst the danger of damage to the cord by the dry needle-point has probably been overestimated.

The choice between glycerin and myodil as a solvent for phenol is a matter of individual preference. If radiological evidence is desirable to confirm accurate positioning then myodil will be selected. However, there is evidence that myodil is very slow to disappear from the site of deposition and tends to form a sludgy deposit around the nerve roots which may render subsequent injections ineffective; therefore, if repeated instillations are probable, glycerin may be preferable. Myodil, however, is less viscous and easier to inject through a fine needle than glycerin, which should be warmed before injection.

Phenol dissolved in glycerin is considered by Brown (1958) to be more potent owing to the phenol being

more readily released into the C.S.F., and he therefore recommends that its use be restricted to the lowest sacral roots. If, however, this reasoning is correct, it is difficult to understand why, since the concentration is more likely to occur towards the tip of the dural sac, the increased potency might not be expected to produce bladder disturbances by involvement of the second, third, and fourth sacral roots.

The action of phenol is selective in that it causes a permanent destruction of the smallest nerve fibres and cells of the posterior root ganglion while leaving the larger fibres comparatively unaffected. Although severe exacerbations of pain, due to some concomitant extension of the disease, such as spontaneous fracture of femoral heads, may penetrate the curtain of analgesia, such "incident" pain is of short duration and can be adequately controlled by drugs.

Experiences with intrathecal phenol have led Maher (1960) to describe two pathways by which pain reaches the central nervous system. The larger fibres, possessing a high-conduction rate and requiring a brisk stimulus, may be responsible for pain of sudden onset, whilst the small non-medullated fibres are responsible for the conduction, much more slowly, of continuous pain. The larger fibres transmit pain quickly to elicit defensive reflexes and may be concerned in incident pain, but it is the smaller fibres which are most susceptible to the action of phenol in the concentrations most commonly used intrathecally.

The causes of failure of phenol to produce analgesia of nerve roots may be due to fibrosis or invasion of nerve elements by tumour cells; radiculitis, giving rise to inflammatory swelling of nerve roots which tend to exclude phenol by filling the root pockets; as well as by the use of inadequate concentrations of phenol or inaccurate posturing. In cases resistant to 5% phenol, Maher obtained success by the addition of small doses of silver nitrate (1/80 gr. (0.8 mg.) in 1 ml.) and found that this addition could also make permanent a temporary phenol effect at the expense of slight meningeal reactions.

Intrathecal phenol, in concentrations higher than 5%, has been used successfully (Nathan, 1959) to abolish the spasticity of paraplegics by destroying the anterior roots. Phenol 10–20% in glycerin is required, but some effects on the posterior roots are inescapable and some loss of sensation is inevitable. Nevertheless, the conversion of spastic to flaccid paralysis and the abolition of spasms in these unfortunate cases can thus be achieved without an operation and renders life much more bearable and nursing easier.

Pain-relief Clinics

"Light is the task where many share the toil."
—HOMER.

In conclusion, let us spare a thought with regard to the establishment of clinics specifically for the treatment of this most insistent of man's afflictions. While we may classify pain clinically into visceral, somatic, or psychogenic compartments, only rarely does the pain fail to affect the psyche, and the psyche the pain.

There is little doubt that, whatever methods one employs to combat intractable pain, the earlier treatment is begun the more effective is it likely to be, and the existence of clinics specifically for this purpose leads to the creation of confidence between patient and doctor which is all-important to success.

Those centres which now operate in Britain are all too few, but their establishment is indicative of an increasing interest among doctors to meet the challenge which severe chronic pain offers.

Anaesthetists have a vital part to play in this sphere; indeed, many of the clinics at present operating owe their existence to the extension of clinical anaesthesia into therapeutic fields. In some the accent may be on nerve-blocking and physiotherapy, in others on drug therapy or the neurosurgical approach, but even the psychotherapist or hypnotherapist cannot be excluded from this field. Such clinics cannot develop as they should without the skill and advice which only a panel of correlated specialists can supply and which is so necessary to meet, and combat, an enemy of such magnitude and resilience.

Summary

The treatment of severe chronic pain merits a new appraisal in the light of recent developments in analgesic drugs and methods of achieving selective action on nerve roots by subarachnoid injections.

The complexity of factors influencing appreciation of pain must be accepted by workers in this field.

The use of morphine might well be delayed or even relegated to the terminal stages of pain in malignant disease.

In the severe pain of primary or secondary cancer, subdural phenol in 5% concentration in lipoid solvents has proved a relatively safe, and sometimes remarkably efficient, therapeutic agent, especially in pelvic and lower-limb growths. The experience gained by anaesthetists of the gravitational control of solutions injected below the arachnoid can be utilized to advantage in this form of therapy.

Life is almost certainly prolonged where the pain of malignant disease is adequately controlled, and this must inevitably rob cancer of much of the dread associated with it.

Pain-relief clinics, successfully operating in some centres, are essential for the early and complete treatment of severe pain.

I wish to thank my medical and surgical colleagues of the Taunton and Somerset and Bridgwater Hospitals for kindly referring cases to me, and Dr. Robert Maher for his unstinting encouragement and advice.

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A new American journal, *DSH Abstracts*, is being published by Deafness Speech and Hearing Publications, and contains abstracts of literature in the areas of deafness, speech, and hearing. It will be published quarterly in January, April, July, and October. Publication was made possible by a training grant provided by the Office of Vocational Rehabilitation, Department of Health, Education, and Welfare. Inquiries should be sent to the Business Manager, Deafness Speech and Hearing Publications, American Speech and Hearing Association, 1001 Connecticut Avenue, N.W., Washington 6, D.C.

THE SKIN AND DISORDERED PORPHYRIN METABOLISM*

BY

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The difficult subject of disordered porphyrin metabolism is bedevilled by a riot of names which have been created to try to distinguish one disorder from another. To add to the confusion the same name, porphyria cutanea tarda, has been used in different senses by different workers. It is therefore clearly necessary to define the criteria by which the types of disorder are distinguished. The classification has been improved, notably by Waldenström (1957), whose scheme I have followed. It should be remembered that the inherited types of disorder are almost certainly separate diseases and represent what Garrod (1923) called inborn errors of metabolism, but that the acquired group, which Waldenström calls porphyria cutanea tarda symptomatica, must still be regarded as a syndrome.

Classification

The two most clearly defined types of porphyria are the congenital and acute intermittent. In *congenital porphyria* there is, according to Watson *et al.* (1951), an inherent defect in the bone-marrow leading to the continuous production of porphyrins, which are excreted in the urine and faeces from a very early age. Apart from the pink or red urine which the subjects void, the disorder is noticed on account of the skin changes, which are confined to the habitually exposed parts, which renew their activity every summer, and which finally lead to severe mutilations. The general health is little affected, but the expectation of life is somewhat diminished. The disease runs a quiet, unremitting course and is probably inherited in a recessive manner.

By contrast, *acute intermittent porphyria* is a disease whose victims are liable to fulminating attacks of a catastrophic nature, including violent abdominal pain, complete constipation, paralyses, mania, and often death. The abnormal metabolites excreted in the urine are the precursors porphobilinogen (Waldenström, 1937) and δ-aminolaevulic acid (Haeger, 1958). The inheritance is dominant (Waldenström, 1956), and examination of the urine of some apparently healthy members of affected families shows that they pass porphobilinogen (PBG) and δ-aminolaevulic acid (ALA) without, as yet, having any symptom—a phenomenon described as latency. The skin is affected in only a few cases, and then by no more than an increase in pigmentation.

Protocoproporphyria, or porphyria cutanea tarda hereditaria, resembles acute intermittent porphyria in that its subjects are liable to similar though usually less severe attacks of abdominal pain, neuropathy, or psychosis, its inheritance is dominant (Tio and Leijnse, 1958; Holti *et al.*, 1958), and latency exists. It differs in three main respects. Firstly, porphyrin, chiefly proto- and copro-, is excreted predominantly in the faeces, except during exacerbations, when the urinary excretion rises at the expense of the faecal (Gray *et al.*, 1948; Macgregor *et al.*, 1952; Wells and Rimington, 1953; Calvert and Rimington, 1953; Holt *et al.*, 1958). Secondly, PBG and ALA are passed, if at all, only in small amount and are most likely to be found at the height of the attack. Thirdly, the skin is conspicuously affected in some cases.

The last type of disorder, *porphyria cutanea tarda symptomatica*, is regarded as acquired, begins in middle life, and is rare in women except among the Bantu (Barnes, 1955), in whom it is commoner in women than in men. The clinical picture is of a seasonal blistering eruption on the exposed parts. Liver disorder, often attributed to the toxic effects of alcohol, but sometimes to supposed nutritional deficiency as in the Bantu, and exceptionally to porphyrin-producing liver tumours (Hamminga, 1951; Tio *et al.*, 1957; Waldenström, 1957), may be the cause of the trouble, but alcoholic bouts can precipitate exacerbations in protocoproporphyria, and since the skin changes can be identical in both diseases every effort should be made to exclude protocoproporphyria before labelling a case as porphyria cutanea tarda symptomatica.

The main distinguishing criteria of the porphyrin disorders are summarized in Table I.

TABLE I.—*Summary of Distinguishing Criteria of Porphyrin Disorders*

	Porphyria			
	Congenital	Acute Intermittent	Protocopro	Cutanea Tarda Symptomatica
Heredity	Prob. recess	Dom.	Dom.	—
Main route of excretion	Urine	Urine	Faeces	Urine
PBG and ALA	—	++	+ or −	—
Presumed site of defect	Bone-marrow	Liver	Liver	Liver
Abdominal pain, neuropathy, psychosis	—	Very severe	Less severe	—

Here I must digress to discuss some of the other names and in particular porphyria cutanea tarda, which has been used in two senses. The name originated with Waldenström (1937), who used it to describe cases of porphyria with skin manifestations of late onset as compared with those of congenital porphyria. He has now subdivided porphyria cutanea tarda into hereditary and symptomatic types, the former being synonymous with protocoproporphyria (Waldenström, 1957), which I prefer. The sense in which Brunsting (1954) uses porphyria cutanea tarda is equivalent to the clinical aspects of Waldenström's symptomatic type, whereas Rimington uses it as identical with protocoproporphyria.

Within any family group the possible clinical forms of protocoproporphyria are of four types: (1) latent; (2) with skin lesions only; (3) with skin lesions accompanied by abdominal pain, neuropathy, or psychosis; and (4) with abdominal pain, neuropathy, or psychosis only. From a *clinical* point of view the type with skin lesions only can be identical with porphyria cutanea tarda symptomatica, and the type with abdominal pain, neuropathy, or psychosis only can be identical with acute intermittent porphyria. Therefore, so long as a clinical classification is adopted confusion is bound to arise. The situation is further complicated by the use of the term "mixed" for cases in which there are skin manifestations accompanying what is clinically an attack of acute intermittent porphyria. It is probable

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that these mixed cases are in reality examples of protocoproporphyria. The possible clinical forms of protocoproporphyria are summarized in Table II.

TABLE II.—*Possible Clinical Forms of Protocoproporphyria*

Manifestation in Individual	Possible Clinical Confusion with	N. American Name
None (latent)	—	—
Skin only	P.c. tarda sympt.	P.c. tarda
Skin + abdominal pain, neuropathy, psychosis	—	Mixed
Abdominal pain, neuropathy, psychosis	Acute i.p.	Acute i.p.

In this connexion there has been one very beautifully worked out family group of porphyrics (Dean and Barnes, 1955) who have so far been difficult to classify. The family are the offspring of an early settler in South Africa who arrived from Holland in 1713. Dean and Barnes traced all the 434 living descendants of the third son of the patriarch's great-grandson. The clinical features of this family group exactly correspond with the possible clinical forms of protocoproporphyria, with a tendency for men to have the skin lesions only, and women to have abdominal pain, neuropathy, or psychosis only, their often lethal attacks usually being precipitated by taking barbiturates. Dean and Barnes, who originally felt that they were dealing with acute intermittent porphyria, later (Dean and Barnes, 1959) compared their cases with some of Waldenström's Swedish cases of acute intermittent porphyria and concluded that the diseases are different. Dean and Barnes's cases behave, in fact, exactly like cases of protocoproporphyria from a biochemical point of view. They suggest calling their cases variegate porphyria, which is far less ugly than protocoproporphyria, and has much to recommend it from the clinical standpoint, since the disease varies so much in its manifestations in the family as a whole. I agree in rejecting porphyria cutanea tarda hereditaria on the grounds that in some individuals the skin is never affected, and in those who are affected the skin lesions are seldom late in appearance.

The conception of porphyria cutanea tarda symptomatica includes those cases originally described as chronic cutaneous porphyria by Szodoray and Sümegi (1944), as bullous and erosive porphyria of the adult by Borda and Campins (1950), as cutaneous porphyria of the adult by Bolgert *et al.* (1953), and as actinic-traumatic bullous dermatosis by Tappeiner and Tirschek (1953).

Types of Skin Changes

So much for the rather difficult matter of classification. My object has been to review the skin changes which occur in the different types of disordered porphyrin metabolism, and the study which follows has been founded on a consideration of cases of porphyria with skin lesions culled from the literature. When it came to assigning cases to types of disorder according to the criteria already described I was in the immediate difficulty that, with few exceptions—for example, Calvy *et al.* (1951)—the families of cases had not been studied nor had the faecal excretion of porphyrin. It was therefore only possible, in general, to assign to protocoproporphyria cases which had definite abdominal, paralytic, or psychotic symptoms. No doubt one or two patients have been included thereby whose symptoms happened to have perfectly ordinary causes. On the other hand, it is inevitable that some will not have been included in protocoproporphyria who really belong there on account of the manifestations of their disease being confined to the skin up to the time of their description.

Since the object was to relate the types of disordered metabolism to the skin changes observed, the cutaneous manifestations were not considered in any way in typing the cases. The inevitable result was a remainder group which contained neither obvious congenita nor obvious protocoproporphyria cases, but which could be expected to contain cases of porphyria cutanea tarda symptomatica as well as incomplete cases of protocoproporphyria, and possibly late cases of congenita as well.

There were 85 cases altogether (Table III), and the skin lesions of all types of porphyria had in common their occurrence on the habitually exposed parts.

TABLE III.—*Occurrence of Skin Lesions on Exposed Parts*

	Totals	Exposed Parts
Porphyria congenita ..	16	16
Protocoproporphyria ..	40	39
Remainder	29	29

That light is essential for the production of the lesions is certain, both because of their distribution and because protection from light prevents their occurrence. Nevertheless, the skin is seldom photosensitive in any obvious sense, for it is unusual to be able to produce lesions experimentally by the use of light, and it seems that prolonged and repeated exposure is necessary as a rule to produce them naturally. This matter is discussed further after the morphology of the skin lesions has been considered.

The skin of the porphyric can be altered in three main ways, apart from pigmentary changes: (1) *blistering*; (2) *mutilating scarring*, and (3) any one or any combination of the triad of *oedema*, *erythema*, and *vesiculation*, hereafter called the O.E.V. reaction.

The blistering tendency resembles epidermolysis bullosa in that the lesions are provoked by such minor activities as bed-making or tying up a parcel, and they usually appear without preceding erythema. It differs in that the feet are spared in shod persons and that sunlight provokes blistering, but it is usual for blistering to be worse in the summer rather than after a particular exposure, unless this has been an exceptionally severe one. It appears that repeated exposures to light in requisite dosage damage the skin, which damage is manifested not only by an epidermolysis-bullosa-like syndrome but also by easy rubbing off of the skin, easy bruising, and delayed healing of the ulcers which follow blistering. The cutaneous vessels share in this damage, with the result that subjection of the skin to an erythema dose of light for the normal individual produces little or no reaction in the porphyric, the wealing effect of histamine is much diminished (Holti *et al.*, 1958), and the histology of the blisters shows virtually no inflammatory reaction. The blisters are followed by superficial scars, milia, and pigmentary changes—usually a blanching of the scar and darkening of the surrounding skin.

The mutilations develop after a long time on the basis of the blistering tendency. The nose and ears are eaten away as in lupus vulgaris, the scalp is scarred, the corneae are scarred, the nails of the fingers dystrophic or shed, the fingers fixed in a claw-like deformity, and the terminal phalanges lost. The old name for this hideous picture was apt—pemphigus leprosus.

The O.E.V. reaction is less common than blistering. The oedema is sometimes sudden and severe and imitates angioneurotic oedema. The addition of erythema, and the malaise which often accompanies this type of reaction, suggests erysipelas, and the occurrence of vesiculation a severe contact eczema.

The distribution of these three types of reaction among the three groups of cases shows that the blistering tendency is common to all but not universal in protocoproporphyria as it is in the other groups (Table IV). Mutilating scarring is typical of congenita

TABLE IV.—*Incidence of Main Types of Change*

	Total	Blistering	Mutilation	O.E.V.
Porphyria congenita ..	16	16	9	1
Protocoproporphyria ..	40	30	1	27
Remainder	29	29	1	6

and the O.E.V. reaction of protocoproporphyria, with a few in the remainder group. It seems likely that the reaction of O.E.V. is confined to protocoproporphyria and that the cases in the remainder group that exhibit it are *formes frustes*, the real nature of which would be revealed by fuller investigation; but this suggestion must await further study. Some cases of protocoproporphyria have never exhibited it, and its presence does not preclude the blistering tendency, for both patterns of reaction can occur in the same patient during the course of the disease.

Exposure to Light in Relation to Skin Lesions

If one now considers the relationship between exposure to light and the production of skin lesions, two patterns emerge. On the one hand, there are aestival recurrences of blistering activity where the variable factor seems to be the quality of light, for in climates where the sun is strong all the year round the blistering activity never ceases (Findlay and Barnes, 1950). On the other hand, there are sporadic bursts of activity in the skin, related to a particular exposure to light, not necessarily a severe one, in which the variable factor seems to be the activity of the disease, and these are typical of protocoproporphyria, and of the O.E.V. reaction in particular. The O.E.V. pattern of reaction is the one which is sometimes obviously photosensitive, and it is the one displayed by the majority of patients who have developed experimental lesions, notably the brother and sister described by Wells and Rimington (1953) and by Magnus *et al.* (1959).

On comparison of cases showing the O.E.V. pattern of reaction with all others (Table V) it is seen that the former are less likely to display seasonal activity and more likely to show sporadic activity in the skin, an obvious relationship between exposure to light and the occurrence of skin lesions, and a demonstrable hypersensitivity of the skin to light. The two patterns of reaction are summarized in Table VI.

TABLE V.—*Relation of Skin Lesions to Light Exposure*

	Total	Seasonal	Sporadic	Obvious Relationship	Experimental Hypersensitivity
O.E.V.	34	12	14	25	10
Others	51	36	6	14	2

TABLE VI.—*Patterns of Reaction to Light*

Pattern of Reaction	The Variable	The Stimulus
Seasonal blistering	Quality of light	Summer
O.E.V.	Activity of disease	A specific exposure

I have shown that patients reacting with O.E.V. are prone to sporadic outbursts of activity in their skin due to enhanced photosensitivity, and that the O.E.V. pattern of reaction is typical of protocoproporphyria. This type of porphyria is known to undergo variations in its activity, and I have already mentioned that during exacerbations urinary porphyrin excretion is increased at the expense of faecal, presumably by some impediment to biliary excretion. It seems possible that the increased sensitivity associated with the O.E.V. pattern of reaction could be due to increase of porphyrin in the blood and tissues, and this suggestion is supported by the far greater incidence of jaundice among O.E.V. reactors (Table VII).

TABLE VII.—*Incidence of Jaundice*

	Total	Jaundice
O.E.V.	34	11
Others	51	2

Magnus *et al.* (1959) have shown that the oedema reaction is due to the presence of porphyrins, and Wells and Rimington (1953) found that the superficial blood-vessels in the dermis are severely affected in histological sections from the oedema reaction, and they and others have described purpura after sufficient exposure. Finally, the historical experiment of Meyer-Betz (1913), who injected haematoporphyrin into his own vein and became an oedema reactor for over two months, is consistent with the idea that the O.E.V. pattern of reaction is due to an increase in blood and tissue porphyrins. This is not the whole story, because some cases of protocoproporphyria never develop the O.E.V. reaction, even though they are jaundiced—for example, Macgregor *et al.* (1952)—and I wonder whether the type of porphyrin may be important or the presence of porphyrin precursor, such as porphyrinogen, which is strongly catalysed by light.

When the activity of the disease abates the patients lose their capacity for reacting by O.E.V. For example, Thomas's (1950), patient, who sat in the open under an overcast sky in August, 1948, and reacted briskly, was able to bathe in the sea and wear short-sleeved dresses with impunity by 1954 (personal communication). This patient's exposure seems to have precipitated an exacerbation of the disease as well as the O.E.V. reaction, and in many reports there is the suggestion that exposure to light increases the production of porphyrins. For example, in the case described by Calvy *et al.* (1951) the patient knew from experience that exposure to the sun made him feel ill and made his urine darker, and he had arranged his life accordingly. Incidentally their paper described what must be protocoproporphyria in three generations, and the histories of the affected members cover all the clinical forms of the disease.

I would like now to describe briefly the other skin manifestations. Hypertrichosis is common in congenital porphyria, especially in females, but seems less frequent in the other types. The scalp hair sometimes darkens as the disease develops. Increased pigmentation occurs in all types of disorder; it is often blotchy and resembles chloasma, is sometimes diffuse, and, very rarely, Addisonian. It reaches its most dramatic degree

when the features, and occasionally the sclerae, are suffused with a coppery, fiery, or cyanotic tinge. Bolgert *et al.* (1953) make a special mention of blotchy pigmentation of the temples in porphyria cutanea tarda symptomatica. In porphyria congenita the teeth erupt pink or purple, and they tend to turn brown.

There are a whole range of changes which imitate other dermatoses, such as acne necrotica, colloid milium, scleroderma, lichenification, and hydroa aestivale. In this connexion it seems likely that cases of hydroa aestivale in which porphyrinuria has been reported have been really cases of porphyria. There seems to be a general tendency in protocoproporphyria for the skin to itch and to develop erythematous lesions followed by vesicles and then crusts, which are often black with blood. Healing of these lesions is more rapid than it is in the lesions associated with seasonal blistering. A warty change or hyperkeratosis of the exposed parts occurs, the skin often looks thickened and coarse, and the normal markings are exaggerated.

Conclusion

My main theme has been that there are, apart from pigmentary disturbance, three major ways in which the skin can be altered in the subjects of disordered porphyrin metabolism. They are blistering, mutilating scarring, and the reaction of oedema, erythema, and vesiculation (O.E.V.). No skin changes occur in acute intermittent porphyria except an increase of pigment. The blistering tendency is common to all other types, mutilation is typical of congenital porphyria, and the O.E.V. reaction of protocoproporphyria. The O.E.V. reaction differs from the blistering tendency in that the former depends upon a temporary greatly increased sensitivity to light, probably brought about by an increase of porphyrins, or porphyrin precursors, in blood and tissues, and the latter depends upon the seasonal quality of light. It seems probable that the skin changes which occur in protocoproporphyria cover a much wider range than those in porphyria congenita and porphyria cutanea tarda symptomatica, but the position can be clarified only when the routine investigation of all cases includes study of faecal porphyrin excretion in the patient and his family.

For the purposes of this paper I have borrowed freely from the work of other people and have contributed no more than a reappraisal of their material. Four of the cases included here have been observed personally, and are as yet unpublished; the remainder I have met only in print. To them, and their physicians, I owe a great debt. Finally, I must acknowledge the most generous help from Professor C. Rimington.

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ANTERIOR AND POSTERIOR PITUITARY FAILURE AFTER HEAD INJURY

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Head injury has been reported as a cause of diabetes insipidus (Porter and Miller, 1948), and less commonly of anterior pituitary failure (Witter and Tascher, 1957). The case presented here is that of a girl in whom diabetes insipidus developed after a minor head injury. She died in hypopituitary coma six years later, and a post-mortem examination revealed unusual pathological features.

Case Report

The patient, born in 1936, had had no serious illnesses in childhood and was quite healthy until the age of 15, when she was knocked down by a car in a road accident. There was only momentary loss of consciousness, but she was admitted to hospital, where *x*-ray examination of the skull revealed no fracture. She was kept in hospital for 10 days and then discharged perfectly well, two scalp wounds having healed.

The patient was next seen two years later complaining of polyuria, polydipsia, and loss of over a stone (6.4 kg.) in weight, and, although a poor witness, she said the symptoms dated from shortly after the time of the accident. There was no family history of any similar trouble. On examination she was seen to be a thin girl with a blood-pressure of 140/90 mm. Hg; no abnormal physical signs were detected. She was a dull, immature type of person, and at first it was thought her thirst might be due to hysteria. However, the diagnosis of diabetes insipidus was made when it was found that her urinary output measured up to 6.5 litres daily, while the specific gravity of the urine remained at 1004 after 24 hours' deprivation of water. Nicotine and intravenous hypertonic saline had no antidiuretic effect, but after an injection of "pitressin" the concentration of urine rose and the volume sharply diminished. The Wassermann reaction and Kahn test were negative and *x*-ray films of the skull and chest were normal. No other abnormalities were found. While in hospital the patient was uncooperative and refused to take pitressin by injection. She was discharged, taking two ampoules of pituitary snuff daily, which was sufficient to control her symptoms.

She was next seen nine months later, aged 18, complaining of vomiting and amenorrhoea. Menstruation had previously been normal since it started at the age of 10. She was found to be pregnant, and in June, 1955, after a normal pregnancy and labour an infant girl was born; there was no post-partum haemorrhage. She was discharged home breast-feeding the baby and taking 3 ml. of pitressin tannate by daily injection.

The patient failed to keep subsequent out-patient appointments and was not seen again for three years, until October, 1958, when she was referred by her own doctor. After the pregnancy menstruation had continued normally for about two years, but there had been amenorrhoea for the previous 12 months. Although she had stopped taking pitressin she no longer complained of thirst or nocturia. On examination she was lethargic and rather plump, the cheeks were flushed and the eyebrows scanty, and the dry skin and facies were strongly suggestive of myxoedema. Her voice was slurred and there seemed to have been a mental slowing since her last examination. The blood-pressure was 90/60 mm. Hg. Breast development was moderate and the pubic and axillary hair were normal. There was no visual field defect and on *x*-ray examination the pituitary fossa appeared normal. Further investigation gave the following results:

		After 120 units A.C.T.H. gel
24-hour urinary sodium	146 mEq ..	28 mEq
" " " potassium ..	55 mEq ..	75.5 mEq
" " " 17-ketosteroids ..	10.7 mg. ..	8.8 mg.
" " " 17-ketogenic steroids	Nil ..	17.4 mg.
Serum sodium	157 mEq/l.	
Serum potassium	5.5 mEq/l.	
Serum cholesterol	375 mg./100 ml.	
Basal metabolic rate	31% below standard	

Anterior pituitary failure was diagnosed, with secondary hypofunction of the thyroid gland, adrenal cortex, and ovaries. Meanwhile the diabetes insipidus had become less severe and the daily urinary volume varied between 2 and 5 litres. Treatment was started with cortisone 25 mg. twice daily, but before any further progress could be made the patient discharged herself from hospital, despite repeated warnings of the possible dangers of her illness.

Three months later, in January, 1959, she was readmitted, having taken no cortisone during the intervening period. She was drowsy, pale, cold, and dehydrated; temperature 93° F. (33.9° C.); blood-pressure 80/50 mm. Hg. Investigations showed: serum sodium, 161 mEq/l.; serum chloride, 135 mEq/l.; blood sugar, 45 mg./100 ml.; blood urea, 51 mg./100 ml.; there was a normochromic, normocytic anaemia; Hb, 8.8 g./100 ml.

It was thought that she was suffering from the effects of panhypopituitarism, the dehydration being the result of diabetes insipidus. Within a few hours of admission her temperature fell to 90° F. (32.2° C.) and she passed into coma.

Treatment was started with 100 ml. of hydrocortisone, 40 g. of triiodothyronine, and 5 I.U. of thyrotrophic hormone in the first 12 hours, and when it became evident that large volumes of urine were being passed 5 units of pitressin tannate in oil was added. Subsequently maintenance doses of these drugs were prescribed as well as deoxycortone acetate and prophylactic penicillin. The patient was slowly warmed to 97° F. (36.1° C.), and the fluid and electrolyte balance maintained via an intravenous "polythene" catheter.

The coma persisted, and when, on the fourth day, there were signs of respiratory obstruction, a tracheostomy was performed. Shortly afterwards the blood-pressure fell to below 80/50 mg. Hg, and was raised with intravenous noradrenaline, which had to be continued for a further three days. By the end of the first week the patient was maintaining a normal temperature without extra external heating and the triiodothyronine was replaced by thyroxine. The persistent anaemia was treated by blood transfusion. Her condition remained unchanged during the second week, but towards the end of the third week she regained consciousness and spoke a few words. However, shortly afterwards a staphylococcal pneumonia developed and despite antibiotics and increased doses of cortisone she relapsed into coma.

Thereafter she gradually lost weight and her general condition deteriorated. During the fifth week head retraction, attacks of trismus, and teeth-grinding developed, and all four limbs became spastic in flexion with bilateral extensor plantar responses. She remained in this state for a further two weeks, punctuated by periods of hyperpyrexia rising to 105° F. (40.6° C.), and finally died six weeks after the onset of coma.

Post-mortem Findings

The body was that of a pale young woman with a tracheostomy opening on the front of the neck. Body build, fat distribution, and breast development were normal. Pubic and axillary hair growth was normal. The *cardio-vascular system* showed no abnormality; the *respiratory system* a severe degree of congestion, especially of the lower lobes; and the *alimentary system* a moderate degree of ascites, but no other abnormality. In the *genito-urinary tract* there was a slight degree of hydronephrosis on the right side; the ureters and bladder and the uterus and tubes

were normal. Both ovaries were atrophic. The *lymphatics* were normal.

Endocrine System.—The pituitary gland *in situ* appeared normal. The stalk was intact and showed no sign of adhesions or of inflammation. The meninges in this area were also normal. On section of the gland the posterior lobe was found to be occupied by hard fibrous tissue. The thyroid gland was smaller than normal, weighing 14 g. The adrenal glands appeared normal and weighed 14 g. together.

Cranium and Contents.—There was no evidence of past head injury or any other abnormality of the skull. The brain was normal except for a feeling of toughness on cutting through the hypothalamus.

Histology

Pituitary Gland (Fig. 1).—There was a slight degree of post-mortem change affecting the anterior lobe, but no other abnormality was present. The posterior lobe and nearly all the stalk had been replaced by fibrous tissue. In the main body of the lobe it was dense and almost acellular, but along the border with the anterior lobe and in the stalk there were chronic inflammatory cells, mainly plasma cells, which in places formed denser foci. The cellular areas also

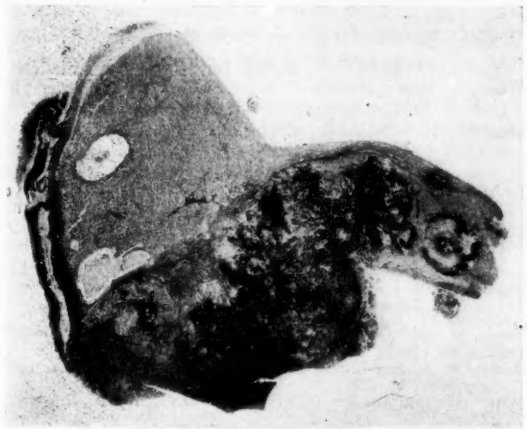

FIG. 1.—Pituitary gland and stalk. (Haematoxylin-Van Gieson. ×8.)

contained fibroblasts—especially numerous in the stalk, where sclerotic changes were not prominent—and macrophages with coarse granules of haemosiderin in their cytoplasm. The only normal structures remaining in the stalk were a thin zone of pars tuberalis with the hypophysial portal vessels anteriorly.

Hypothalamus.—The cellular fibrous tissue seen in the pituitary stalk extended upwards to the median eminence and the floor of the third ventricle and along part of its lateral walls. Dense strands of collagen were present between which the plasma-cell infiltrate tended to form perivascular foci. Haemosiderin-containing macrophages could be found throughout this abnormal tissue, which also contained numerous fibroblasts. Mrs. E. Beck examined sections of the hypothalamus and indicated the probable extent of the lesion (Fig. 2). It involved the suprachiasmatic region and the walls of the optic recess. The mamillary bodies, the ventro-medial hypothalamic nuclei, part of the dorso-medial nuclei and the medial part of the lateral hypothalamic nuclei had been destroyed. The optic chiasma, pre-optic nuclei, and diagonal band nuclei were normal, and the subthalamic and red nuclei were unaffected. The supraoptic and paraventricular nuclei were devoid of nerve cells. No trace of neurosecretory material was found either in the hypothalamus or in the neurohypophysis.

In the *thyroid gland* the acini were well filled with colloid, the lining cells were flattened and appeared to be inactive, and there was no fibrosis or lymphocytic infiltration. The *adrenal glands* were normal except for some post-mortem change. Both *ovaries* were completely atrophic; serial sections showed no evidence of follicle formation, and the sclerotic remains of corpora lutea seen appeared to be very old. The endometrium of the *uterus* was thin and inactive; there was an increase in stromal collagen. The *liver* showed marked centrilobular fatty infiltration. The *lungs* were severely congested but there was no other abnormality. The *kidneys* showed a mild degree of acute pyelonephritis.

Discussion

Traumatic Diabetes Insipidus

The true incidence of diabetes insipidus due to head injury is not known. Blotner (1951) believes it to be greatly overestimated and cites cases with a history of concussion in which the lesion was later found to be a brain tumour. There was a history of trauma in 6 of his 50 "idiopathic" cases, but he did not regard this as significant. Pickles (1947) found four cases of diabetes insipidus in 2,500 patients with head injuries.

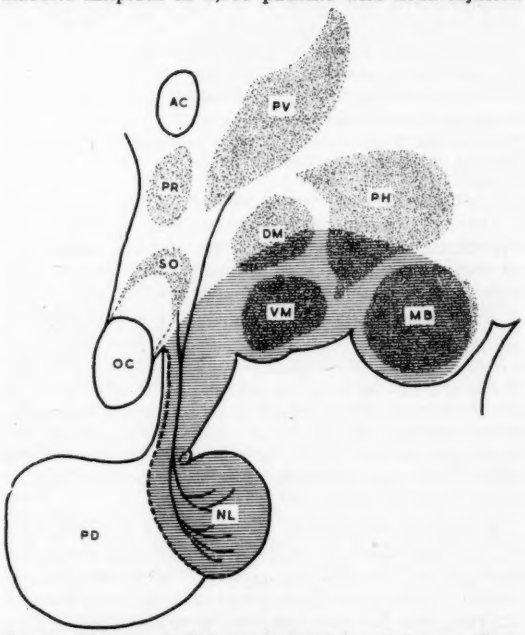

FIG. 2.—Diagram of pituitary gland and hypothalamus. Hypothalamic nuclei are represented by stippled areas and the extent of the histological lesion by hatching. AC=Anterior commissure. DM=Dorso-medial nucleus. MB=Mamillary body. NL=Neural lobe. OC=Optic chiasma. PD=Pars distalis. PH=Posterior hypothalamic nucleus. PR=Pre-optic nucleus. PV=Paraventricular nucleus SO=Supraoptic nucleus. VM=Ventro-medial nucleus.

three of which cleared up within four months. Porter and Miller (1948) found 13 cases of diabetes insipidus in 5,000 cases of closed head injury and collected five additional cases. The condition was not associated with minor injury. Of 18 cases, 13 had post-traumatic amnesia for over a week and 12 had a fracture of the skull, while there was olfactory damage in 11 cases, and optic nerve and tract damage in 6. In one case there was anterior pituitary dysfunction and another developed Fröhlich's syndrome. Porter and Miller considered the lesion causing diabetes insipidus to be in the pituitary stalk, attributable to stretching at the time of injury, and they suggest that the rarity of permanent traumatic diabetes insipidus is due to the high mortality of injuries in this area.

Very little is known of the pathology of post-traumatic lesions of the hypothalamus and pituitary. Henzi (1952)

reported a case of diabetes insipidus arising in a girl aged 11 after a severe head injury. Polyuria remained continuous until the patient's death at the age of 60, during which time she had seven pregnancies. At necropsy the pituitary gland was found embedded in scar tissue and there was no sign of a stalk. Microscopically there was scarring involving the posterior lobe and the tuber cinereum, and extending around the supraoptic nuclei, in which the number of cells was reduced. There was also some reduction in the cells of the paraventricular nuclei. The anterior lobe appeared normal.

Beck and Daniel (1959) reported nine cases that had undergone hypophysectomy or pituitary stalk section for the relief of cancer, in all of which a barrier had been placed between the hypothalamus and the pituitary fossa. In those cases surviving only a few weeks a venous infarct was found in the proximal stump of the stalk at necropsy. Cases examined 2 to 26 months after operation were found to have regenerated nerve fibres in the stump, and some of these contained neurosecretory substance. Although signs of the old infarct, such as haemosiderin-containing macrophages, were present, the impression was of a regenerating posterior lobe in the proximal stump.

Hypothalamus and Anterior Pituitary

There is much experimental evidence that the hypothalamus controls the activity of the anterior lobe of the pituitary, and thereby the gonads, thyroid, and adrenal cortex, through the hypophysial portal vessels of the pituitary stalk (Harris, 1955a). It is probable that the nerve fibres from the hypothalamus liberate a humoral substance which is carried by the portal vessels to the anterior lobe. Thus trauma to the pituitary stalk interferes with anterior-lobe function by damaging the portal vessels. Daniel *et al.* (1959) have shown that such damage can result in infarction of the anterior lobe. This might possibly be followed by regeneration (Daniel and Prichard, 1958).

The results of electrical stimulation of different areas of the hypothalamus suggest localization of control of secretion of the different pituitary hormones (Harris, 1955b). Damage to these areas may result in a selective disorder of function in the anterior lobe. Thus inflammatory and neoplastic lesions of the posterior part of the hypothalamus are known to produce effects such as sexual precocity and hypogonadism (in Fröhlich's syndrome), which must be mediated through the anterior pituitary, although the gland itself is not involved by the lesion and appears histologically normal.

Conclusion

The findings in the present case are not easily interpreted in the light of previous observations. The initial head injury was not severe, but its time relation to the onset of the disease suggests that it was the cause. No alternative aetiological factor was discovered. It is likely that traumatic interruption of the supraoptico-hypophysial tracts produced diabetes insipidus soon after the injury and that retrograde degeneration resulted in the disappearance of nerve cells in the supraoptic and paraventricular nuclei. Anterior pituitary function remained apparently normal after the accident and throughout the subsequent pregnancy and lactation. This makes it unlikely that the anterior lobe could have been damaged at the same time as the neurohypophysis. Hypothalamic control of the anterior lobe must also have been normal at this time. The presence of haemosiderin throughout the hypothalamic lesion, as well as in the posterior lobe, suggests the occurrence of either haemorrhage or infarction after the injury, but the subsequent evolution of the lesion is difficult to determine. Fibrosis in the central nervous system is unusual, and it may be that with the gradual spread of scarring in the hypothalamus control of anterior pituitary activity progressively weakened until, despite the presence of an apparently normal gland with an intact blood supply, hormone secretion diminished and the clinical picture of anterior pituitary failure resulted.

Summary

An account is given of the case of a girl of 15 in whom diabetes insipidus occurred after a head injury. She later developed anterior pituitary failure and died six years after the accident in pituitary coma. Post-mortem examination revealed widespread sclerosis throughout the neurohypophysis and the hypothalamus, but the anterior lobe of the pituitary appeared normal. Traumatic pituitary failure is discussed and an attempt is made to interpret the features of this case.

We thank Dr. C. A. Young for permission to publish this case, and Professor P. M. Daniel, Mrs. E. Beck, and Dr. R. R. Wilson for their help and encouragement. The illustrations were prepared by Mrs. E. Beck.

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SEPTICAEMIA CAUSED BY AN ORGANISM RESEMBLING PASTEURELLA SEPTICA AFTER A DOG-BITE

BY

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Pasteurella septica is a Gram-negative coccobacillus commonly found in the throats of animals. Schipper (1947) isolated the organism from 14 of 102 trapped wild Norway rats; Smith (1955) found that 61 of 111 healthy dogs were carriers; and the pig, the cat, and the ox are also known to harbour the organism. Apart from its commensal habits, it is also an important pathogen of animals and birds, the cause of haemorrhagic septicaemia, which is highly contagious and usually fatal. Guinea-pigs, rabbits, and other animals inoculated by Schipper succumbed within a day, and he stressed that the possibility of a rat-bite should always be considered when domestic animals die suddenly.

Whereas human infection has curiously never been attributed to rat-bite, there are on record many cases which followed the bites and scratches of other animals,

especially the cat and the dog. Characteristically, the wound fails to heal, signs of lymphangitis and lymphadenitis appear, and abscesses may form repeatedly despite local treatment and the use of antibiotics (Mautner and McIntyre, 1956). Byrne *et al.* (1956) believed that the sharp fangs of a cat were more likely to cause osteomyelitis than the blunt teeth of a dog, though at the time their paper was published only four cases of infection from dog-bite had been recorded (Emson, 1957).

The organism when isolated from the sputum in bronchiectasis (Needham, 1948; Cawson and Talbot, 1955) is of doubtful pathogenicity, but it may give rise to empyema thoracis (Horne and Berlyne, 1958) and to chronic sinusitis (Bartley and Hunter, 1947). It has even been found in the nose in the absence of symptoms (Wilson and Miles, 1955), purulent meningitis (Regamey, 1938) or brain abscess (Svendsen, 1947) being a potential sequel of operation or injury in such cases.

The accompanying table was prepared at the Epidemiological Research Laboratory of the Public Health Laboratory Service from reports submitted by bacteriologists in public health and hospital laboratories in England and Wales, and it is reproduced by permission of the Director of the Service. It shows that *P. septica* is often isolated from human wounds resulting from cat- and dog-bites, and that of the two animals the dog is now to be incriminated at least as often as the cat. There is little doubt that in these cases the organism is pathogenic, but the pathogenic significance of the isolations from the other sites shown in the table is doubtful.

Isolations of Pasteurella septica in 1957, 1958, *and* 1959*

Source from Which the Organism was Isolated	No. of Cases
Wounds from dog-bites	48
,, ,, cat-bites	33
,, ,, cat-scratches	15
"Wounds" not further described	5
The respiratory tract†	51
Meningitis after a head injury	1
Brain abscess secondary to otitis media	1
Temporo-sphenoidal abscess	1
Ear swabs	3
Antrum washouts	2
Vaginal swab	1
Urine from a case of cystitis	1
Not stated	3
	165

* Unpublished information from reports made by bacteriologists in the public health and hospital laboratories in England and Wales to the Director of the Public Health Laboratory Service.

† So far as the records show, these isolations were from patients with chronic bronchitis or bronchiectasis.

It appears that septicaemia due to *P. septica* has not previously been known to follow a dog-bite.

Case Report

First Hospital Admission

An unmarried comptometer operator aged 30 was admitted to King George Hospital, Ilford, on June 23, 1959. On June 5 she had accidentally trodden on her dog and in return had been bitten on the left foot. Though antiseptic dressings and poultices were applied, the foot became inflamed, and on June 18 she had an attack of shivering, felt unwell, and vomited twice. Two days later she awoke with a tender swelling in the left side of the neck, and on the day of admission, while the pain in her foot had improved, her left thigh was tender and stiff. She also had aches and pains elsewhere, especially in the arms and hands.

There was no previous history of serious illness, but it may be significant that in 1952 she had been treated for allergic rhinitis with a series of desensitizing injections.

On examination she looked ill, was pale and also slightly jaundiced. Her temperature was 103° F. (39.4° C.). She was drowsy without neck-stiffness, and her respirations were deep and sighing. A swelling in the left side of the neck obliterating the supraclavicular fossa was attributed to enlarged lymph nodes with periadenitis. Two spider naevi on the right hand which had been present since childhood had now enlarged and were pulsatile on light compression. On the inner aspect of the left foot there was an inflamed puncture wound 1 cm. long with a small pustule on its edge. Two smaller superficial abrasions were present on the dorsum of the foot, the whole of which was swollen. Lymphangitis extended from mid-calf to the popliteal fossa, and the posterior aspect of the thigh was tender and indurated. There were a few small non-tender lymph nodes in the left groin. The spleen and liver could not be felt.

Investigations and Progress

Three blood specimens were taken at hourly intervals before starting antibiotic treatment, and in addition a swab from the pustule on the left foot. The first and third blood specimens were sterile on culture, but an organism closely resembling *P. septica* was grown from the second and from the pus swab. A similar organism was also isolated from the dog's mouth (see Appendix). The haemoglobin on admission was 8.2 g./100 ml., white blood count 7,400/c.mm. (polymorphs 70%, lymphocytes 30%), and serum bilirubin 3 mg./100 ml. A chest *x*-ray film showed patchy areas of consolidation in both lower lung zones. Lumbar puncture the next day showed the cerebrospinal fluid to be normal, and agglutination reactions for *Leptospira icterohaemorrhagiae* and *Leptospira canicola* on June 26 and July 21 were negative.

Intramuscular penicillin, four million units six-hourly, was given from June 23 to July 24, and oral erythromycin, 250 mg., six-hourly from June 29 to August 28. At first the patient's condition worsened. She also developed painful swelling of the wrists and hands and a small pustule appeared on the dorsum of the right great toe. This was aspirated on June 30 but proved sterile. The jaundice deepened; on July 2 swelling of the legs was noted, and on the following day there was extensive oedema of the trunk with signs of ascites. Diarrhoea with incontinence of faeces lasted for five days, and during this time the patient was semicomatose. No pathogens were isolated from the stools.

Biochemical tests confirmed the presence of liver disease. July 3: Serum bilirubin, 6.8 mg./100 ml.; alkaline phosphatase, 10 units; thymol turbidity, 15 units; zinc sulphate turbidity, 25 units. Total plasma proteins, 7.3 g./100 ml. (albumin 2.4 g., globulin 4.9 g.). July 15: Serum bilirubin, 2.3 mg./100 ml.; alkaline phosphatase, 25 units; thymol turbidity, 10 units; zinc sulphate turbidity, 24 units. Total plasma proteins, 6.6 g./100 ml. (albumin 2.3 g., globulin 4.3 g.).

The liver was at no time enlarged or tender, and on July 15 a biopsy, using a Menghini needle, showed only mild focal lymphocytic, sometimes polymorphonuclear, portal infiltration, with no great intralobular Kupffer cell reaction. The lobular pattern was retained and no certain evidence of cirrhosis was found. A portion of the specimen sent for bacteriological examination was sterile.

After two weeks the jaundice and oedema lessened and the naevi on the right hand had reverted to their original size. The joint symptoms improved, the wound on the left foot healed, and the bubo in the neck disappeared. In addition, a further chest *x*-ray film showed resolution of the opacities in the lungs. Pain in the left leg and low-grade fever continued, however, until July 18, when a large sterile abscess was drained from the posterior aspect of the thigh. Because of a persistent normochromic anaemia (haemoglobin 46%), 1 pint (570 ml.) of blood was transfused on July 26, the patient eventually being discharged home on August 28, 12 weeks after the initial injury.

Second Hospital Admission

On January 7, 1960, the patient was readmitted. Though she had gained weight and had returned to work she had

continued to complain of tiredness with occasional swelling of the legs. Prior to admission a rise in serum antibody titre had been demonstrated (see Appendix). The liver-function tests had also remained abnormal. December 31, 1959: Serum bilirubin, 2.8 mg./100 ml.; alkaline phosphatase, 11.3 units; thymol turbidity, 13.6 units; total plasma proteins, 8.5 g./100 ml. (albumin 3.8 g., globulin 4.7 g.). On the same day the haemoglobin was 12.5 g./100 ml., white blood count 5,000/c.mm., and erythrocyte sedimentation rate 5 mm. in 1 hour (Westergren).

While she was in hospital there were no abnormal findings other than slight jaundice, and she was afebrile throughout her stay. On January 8 liver biopsy was attempted, again with a Menghini needle, but the fragment of liver tissue obtained was too small to base a diagnosis on it.

On January 11 laparotomy was performed, the liver, which was of normal size, showing the coarsely nodular and irregular appearance of post-necrotic cirrhosis. Both lobes were involved and there was no evidence of liver abscess. Microscopical examination of a large nodule taken from the edge of the right lobe showed hyperplastic parenchyma and in parts retained a lobular pattern, with interspersed extensive fibrous tissue heavily infiltrated with inflammatory cells. These appearances suggested post-necrotic cirrhosis.

Post-operatively her progress was uneventful. Three months later her ankles were still inclined to swell in the evenings, but there were no other symptoms.

Comment

Though *P. septica* septicaemia can follow seemingly trivial injuries (Bearn *et al.*, 1955), it is fortunately rare. For despite the organism's *in vitro* sensitivity to many antibiotics (Gorzynski and Neter, 1953), which will protect animals from otherwise lethal invasion (Needham, 1948), bacterial resistance has been shown to develop rapidly in humans (Mautner and McIntyre, 1956), and antibiotics alone may not eradicate the established infection.

In one patient who died within 10 days (Peltier *et al.*, 1938) the source of infection was unknown. Another (Rivoalen, 1936) had been mauled by a panther, but had the good fortune to survive after a prolonged febrile illness; and in yet another (Bearn *et al.*, 1955) septicaemia was attributed to a cat-bite, the infection in this case being effectively cured with penicillin and streptomycin. On two occasions puerperal sepsis may have been responsible. Thus Robinson's (1944) patient developed septicaemia during the eighth month of pregnancy and miscarried within three days, and Pizey's (1953) patient was a 3-weeks-old infant with multiple pyarthroses.

Cirrhosis of the liver would appear to increase the risk of septicaemia during *P. septica* infection. Necropsy on one patient (Peltier *et al.*, 1938) revealed a cirrhotic liver containing at least four abscesses the size of pigeon's eggs; another (Bearn *et al.*, 1955) had previously undergone a portocaval anastomosis for cirrhosis; and in the patient described above the diagnosis of post-necrotic cirrhosis was established at laparotomy. Sherlock (1948) showed that the progression from acute hepatitis to established cirrhosis can occur within 47 days. Yet the absence of cirrhosis in the first biopsy specimen obtained from this patient does not prove that it develops subsequently, for it is in the post-necrotic variety that blind biopsy is most likely to fail (Braunstein, 1956). Furthermore, the changes in serum protein early in her first admission favoured long-standing liver disease, a raised serum globulin being a notable feature of the post-necrotic cirrhosis of young women (Bearn *et al.*, 1956).

The coexistence of cirrhosis with infection suggests the gut as an alternative portal of entry (Whipple and Harris, 1950), and that pasteurellosis can be enteric was shown by Ludlam (1944), who isolated the organism from an appendicular abscess. Schlecht (1931) also grew pasteurella from the duodenal contents of a patient with severe hepatitis who, because he had eaten chicken—recalling in retrospect its unpleasant taste—was presumed to have been infected with *P. aviseptica*. No other instances of primary hepatitis due to the organism seem to have been recorded, however, and the possibility of pre-existing cirrhosis in Schlecht's patient cannot be ruled out.

Circulating antibodies are not usually found during local infection with *P. septica* (Bartley and Hunter, 1947; Brunsdon and Mallett, 1953), although Allott *et al.* (1944) demonstrated agglutinins in the serum of a patient with an infected dog-bite to a titre of 1 in 80, and in Ludlam's (1944) patient with an appendicular abscess the titre was 1 in 240. In systemic infections, on the other hand, a vigorous antibody response might be expected, as in Robinson's (1944) patient, in whom the titre was 1 in 640. In the present case the surprisingly low titre of 1 in 160 was at first obtained. This was probably not entirely due to the delay in performing the investigation, for Ludlam's (1944) results were noted two months after apparent recovery. In the early stage an excess of circulating antigen may have neutralized all available antibody, or, alternatively, severe liver disease may have impaired antibody production. Yet even more unaccountable was the later rise in titre, and while a persistence or recrudescence of infection would provide an explanation for this, there was no evidence clinically to support it.

The most recent account of wound infection with *P. septica* due to dog-bites is given by Lee and Buhr (1960). They suggest that penicillin should be prescribed prophylactically to all patients with serious dog-bites, and particularly to those whose bites have been sutured. This precaution would appear to be well justified, especially in patients who also happen to have liver disease.

Summary

A patient suffering from post-necrotic cirrhosis of the liver developed septicaemia caused by a pasteurella-like organism following a dog-bite. The infection responded to penicillin and erythromycin after a large abscess had been drained from the left thigh. Though septicaemia due to *Pasteurella septica* is rare in man, it has been associated with cirrhosis of the liver on at least two previous occasions.

The organism isolated resembled closely *P. septica* but differed from the accepted description of that organism in that it fermented lactose and agglutinated to only low titre with a specific pasteurella antiserum. Neither of these unusual features, however, excludes it from the *Pasteurella* group.

I am grateful to Dr. T. F. Elias Jones and Dr. R. J. Henderson, Director of the Public Health Laboratory, Worcester, for their help in investigating the organisms isolated; to Dr. H. K. Weinbren for his reports on the liver biopsies; and to Dr. W. Charles Cockburn, of the Epidemiological Research Laboratory, Colindale, for the preparation of the Table.

APPENDIX

Morphological and Other Characteristics of the Three Strains of Organism Isolated.—PS: From pustule at site of injury on June 23. BC: From blood culture on June 23. D: From dog's mouth, July 1.

Morphology.—A short, oval coccobacillus with rounded ends, about 1.5 by 0.5–0.8 μ, occurring singly, in pairs, and in short chains. Pleomorphism noted in subculture and increased with repeated subculture. It stained Gram-negative; bipolar staining was not a feature and no capsule was seen. (The organism was not observed in tissue-smears.)

Cultural Characters.—Aerobic and anaerobic at room temperature and at 37° C. on ordinary media but not on media containing bile salts. Colonies on agar and blood-agar after 24 hours were small (1–2 mm. diameter) translucent greyish-white disks. No haemolysis seen. No motility in liquid media.

Biochemical reactions to the three strains (PS, BC, and D) were: Glucose +, lactose +, dulcitol −, sucrose +, mannitol +, maltose +, indole +, urease −, gelatin liquefaction −.

Sensitivity to Antimicrobial Agents (Disk Diffusion Method).—

	Concentration per Disk	Zone of Inhibition (Diameter)	
Penicillin	2·5 units	21 mm.	Highly sensitive
Erythromycin	10 μg.	21 ,,	
Chloramphenicol	40 ,,	23 ,,	
Tetracycline	10 ,,	17 ,,	
Sulphafurazole	1 mg.	25 ,,	
Nitrofurantoin	10 ,,	17 ,,	
Novobiocin	10 μg.	13 ,,	Moderately sensitive
Streptomycin	80 ,,	0 ,,	Resistant
Neomycin	100 ,,	0 ,,	
Bacitracin	5·5 units (100 μg.)	0 ,,	

Serum Agglutination Reactions.—These were as follows:

	PS	D
Patient's serum July 29	1/160	1/160
,, ,, October 29	1/80	1/40
Control serum	1/20	1/20
Patient's serum, December 22	1/1,280	1/20
Control serum	1/10	Less than 1/10

Pathogenicity to Laboratory Animals.—PS: Killed a mouse in 24 to 36 hours and caused an abscess at site of inoculation in a guinea-pig in seven days. D: Killed a mouse in seven days. Non-pathogenic to guinea-pigs. BC: Not done.

Reaction with Specific Antisera.—PS and D: No agglutination titre obtained higher than 1:20.

It will be seen that the organism, though closely resembling *P. septica,* differed from it in fermenting lactose and in failing to agglutinate with a specific pasteurella antiserum except in very low dilution. Neither of these differences can be taken too seriously. In the past, several strains fermenting lactose have been isolated from animals, and more recently a group of lactose-fermenting strains possessing haemolytic activity have been defined. Agglutination reactions with members of the *Pasteurella* group are often very irregular, varying sometimes even from day to day with subcultures of the same organism. The general properties of the strain described here, taken in conjunction with its pathogenicity for mice and guinea-pigs, render it justifiable, in the absence of more detailed investigation, to include it tentatively in the *Pasteurella* group.

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ANABOLIC HORMONES IN DERMATOMYOSITIS

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Spontaneous remission and relapse are not uncommon in dermatomyositis, making assessment of the results of treatment difficult. It is apparent from the many remedies listed that no single treatment has been successful. Since their introduction the corticosteroids have been most frequently prescribed, but, while some authors have claimed that these have revolutionized treatment in this group of disorders (Walton and Adams, 1958), others have found their effects to be slight or frankly disappointing (Ragan, 1950; Anderson, 1952; Gross, 1952; Kierland *et al.*, 1952; Wedgwood *et al.*, 1953; Wilson, 1954; Smith, 1955).

We report here two cases of dermatomyositis in which remission occurred after the use of anabolic hormones.

Case 1

Mrs. A, a schoolteacher aged 36, was admitted to hospital in May, 1957, with an acute febrile illness associated with nausea, diarrhoea, and myalgia. On examination she was seen to be of average build, with a

FIG. 1.—Case 1. Section showing widespread necrosis of muscle fibres with aggregations of inflammatory cells. (×400.)

widespread erythematous rash. There was profound generalized muscle-weakness without loss of deep reflexes. A partial thyroidectomy had been performed in 1944 for thyrotoxicosis, and, although clinically she was euthyroid, slight residual exophthalmos was present. A coarse pleural friction rub was audible at the base of the left lung. The relevant findings at this stage were as follows. Urine: albumin, 2 parts, Esbach; granular casts present. Blood urea, 30 mg./100 ml.; E.S.R., 54 mm. per hour (Westergren); W.B.C., 14,000/c.mm. No L.E. cells were present in a suitable preparation. Biopsy showed widespread necrosis of muscle fibres, with diffuse round-cell infiltration and aggregations of inflammatory cells, mainly plasma cells. The arteries were unaffected (see Fig. 1).

Prednisolone 60 mg. a day and A.C.T.H. 40 units a day were given with some improvement, but over the next few months relapse occurred on each occasion that the dose was reduced. After adding norethandrolone ("nilevar") to this regimen there was a more sustained improvement in muscle power, and she became able to walk. On discharge home she left the district but remained well for four months, at the end of which period norethandrolone was stopped. Although oral corticosteroids were continued, within a week muscle-weakness again became apparent and progressive. Four months later, when completely bedridden, norethandrolone was restarted, but the response was slight and unsustained.

She was readmitted to our wards at this stage. There had been considerable deterioration. Muscle-weakness was so pronounced that she was unable to lift herself from the bed, and had difficulty in feeding herself. Laboratory findings were: no albuminuria; creatinuria, 1.8 g. a day; E.S.R., 34 mm. per hour (Westergren); total serum proteins, 6.9 g./100 ml. The electrophoretic pattern showed a hyperglobulinaemia due to an increase in the α_2 and γ fractions. The E.C.G. was normal. Radioiodine assay of thyroid function gave normal results.

While corticosteroids were continued in the same dosage, norethandrolone was replaced by another anabolic hormone, methandienone ("dianabol") 30 mg. daily. Over the next three months progress continued, so that at the time of dismissal she was able to rise from a chair and walk unaided. Six months later she was on maintenance doses and was managing light housework.

Case 2

Miss B, a schoolteacher aged 45, had been unwell for six weeks before her admission to hospital in April, 1959, with heaviness and aching in her limbs. Swelling of the face, arms, and legs had been present for two weeks, and shortly after admission an erythematous rash developed over the trunk. Apart from marked muscle-weakness, which prevented her from raising her arms or sitting up unsupported in bed, examination was negative. Laboratory findings were: urine, a trace of albumin; a catheter specimen was sterile but showed granular casts; creatinuria, 1.7 g. a day. Haemoglobin, 10.7 g./100 ml; W.B.C., 16,000/c.mm.; E.S.R., 26 mm. per hour (Westergren); blood urea, 36 mg./100 ml. L.E. cells were not found after several examinations. Chest *x*-ray films and E.C.G. were normal. Total serum proteins, 7.4 g./100 ml. The electrophoretic pattern showed a hyperglobulinaemia due to an increase in the α_2 and γ components. The first muscle biopsy was normal, but the second showed extensive necrosis of muscle fibres (see Fig. 2).

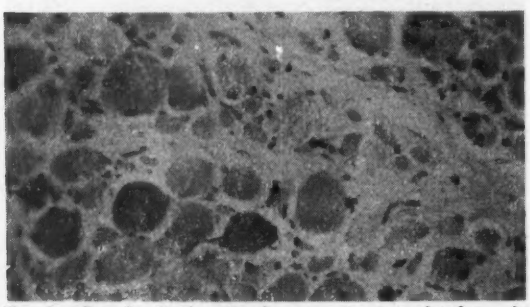

FIG. 2.—Case 2. Section showing extensive necrosis of muscle fibres. (×400.)

Despite treatment with 60 mg. of prednisolone daily and 40 units of A.C.T.H. gel weekly, her condition deteriorated. Dysphagia and weakness of the respiratory muscles developed, complicated by a respiratory infection not controlled by antibiotics. Three weeks after admission a tracheotomy was performed as an emergency measure, and the upper respiratory passages were cleared of much secretion and mucus. The extreme muscle-weakness persisted.

Methandienone was started, 30 mg. daily, two months after admission. After 10 days' treatment a definite and sustained improvement in muscle power became apparent, allowing the removal of the tracheotomy tube. At the time of discharge she was ambulant, and her progress as an outpatient has been maintained. She has returned to full-time teaching and, six months after leaving hospital, remained well. Maintenance doses of prednisolone and methandienone have been continued.

Discussion

Corticosteroids and A.C.T.H. have been the mainstay of treatment of the polymyositis group of diseases, but the results of therapy have been variable and unpredictable, particularly in the subacute and chronic forms (Ragan, 1950; Anderson, 1952; Gross, 1952; Kierland *et al.*, 1952; Wedgwood *et al.*, 1953). As they were the accepted form of treatment, A.C.T.H. and prednisolone were given in adequate doses in both cases throughout. In the first case there was evidence of some remission, but this was not sustained, and attempts to reduce the high dosage of corticosteroids resulted in an acute exacerbation of muscle-weakness. There was steady deterioration in the second case despite corticosteroid therapy, so that emergency tracheotomy became necessary.

We thought it rational to use an anabolic hormone in dermatomyositis because, although the histological picture is largely one of muscle-fibre degeneration and inflammatory cell infiltration, there is also characteristically present regeneration of muscle (Walton and Adams, 1958), and it seemed that the anabolic hormones would aid this process. In addition, their anabolic property would counteract the katabolic effect of long-term corticosteroid therapy.

Testosterone has been tried in dermatomyositis with variable results. Wedgwood *et al.* (1953) stated that testosterone was "possibly helpful" in 10 out of 12 cases that received it, but thought that orthopaedic treatment and physiotherapy were more effective. Where there was rapid destruction of muscle mass, Black and Bunim (1958) employed testosterone in large doses, and found that in some cases there was an increase in weight and muscle strength. On the other hand, Garcin *et al.* (1955), in their review of polymyositis, thought that testosterone was of doubtful value. In addition, the virilizing property of testosterone precludes its long-term use, particularly in females and pre-pubertal males.

In the past three years a number of steroid compounds have been produced which are predominantly anabolic and have little virilizing effect. One of the first of these agents was norethandrolone, but recently methandienone has been claimed to be the most effective anabolic agent orally, and the least androgenic (Foss, 1959).

While corticosteroid therapy was maintained in both our cases, methandienone was introduced, and improvement occurred. In the first patient muscle-weakness regressed in a slow but sustained fashion over a period of months, whereas in the second patient the improvement was more dramatic, and was evident in the first 10 days of treatment. While we may have observed the natural remission of the disease in these patients, its direct relationship to the start of anabolic hormone suggests that it was drug-induced. We consider that anabolic hormones were of value in the cases described and are worthy of further trial in dermatomyositis.

Summary

Two cases of dermatomyositis are described. Although the results of corticosteroid therapy were disappointing, improvement occurred in both cases after the use of methandienone, an anabolic hormone.

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SCHISTOSOMIASIS OF THE SPINAL CORD

REPORT OF A CASE

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Schistosomiasis of the cord has been infrequently reported. It is therefore considered worth while reporting a further case.

Kane and Most (1948) reviewed the literature up to 1944. They recorded 24 cases of cerebral complications of schistosomiasis, of which 14 were due to *S. japonicum*. Two authenticated cases of myelitis due to *S. haematobium* and two due to *S. mansoni* had been described during this period. They comment on the tendency of *S. japonicum* to affect the brain and of *S. mansoni* and *S. haematobium* to affect the cord. Since their paper further cases of spinal-cord involvement have been reported sporadically.

Gama and de Sá (1946) record a case operated on for suspected spinal tumour. A cystic swelling at the second lumbar segment was removed from which *S. mansoni* eggs were isolated. The neurological signs were not affected. Raper (1948) records the finding, at necropsy on an African soldier, of a schistosome in a dense scar compressing the thoracic cord. Two years previously the patient had been offered but had refused surgery for a suspected spinal-cord tumour. Gelfand (1950) reported a personal case in which *S. haematobium* eggs were found in the cord. He comments on the frequency in which schistosome ova of both species are found on digestion of the brains of cases of schistosomiasis, but found ova only in one of the 25 cords examined. Ross *et al.* (1952) report a case of *S. mansoni* of the cord discovered at operation for suspected tumour. The patient improved after operation and antimonial therapy. Horrax *et al.* (1958) describe a case of *S. mansoni* granuloma of the cord which was operated on for suspected spinal tumour.

There are at least four further cases of cord involvement with schistosomiasis in the South American literature not available to us.

Case Report

A European man aged 73 had been a pilot in the first world war. After a flying accident in 1918 he had had an arthrodesis of his right hip and an ankylosis of the right knee-joint. Despite this he had been very active and had actually been playing tennis not very long before the present illness. In July, 1958, he fell and sustained severe bruising of his back and left hip. After this his wife thought he did not walk so well and that his left foot turned in more. Before his arrival in Uganda he had spent some time in Southern Rhodesia and then some months in Tanganyika.

Ten days before admission he had motored up 1,400 miles (2,250 km.) from Tanganyika, driving himself all the way. He complained of stiffness and cramps in his legs. He attended the out-patient department. No abnormalities were noted. A white count at this time was normal. Five days before admission he had another fall; he was unable to get up and was helped into bed. He had some difficulty in moving his legs and had pain in his legs and lower abdomen, but attributed this to the fall.

After this he found difficulty in passing urine and had to strain. The same day he had an involuntary movement of the bowels. Two days before admission he developed retention with overflow. The day before admission he became completely unable to move his legs.

On admission he was an elderly alert man. He had a blood-pressure of 180/100. C.N.S.: The cranial nerves and upper limbs were normal. There was a band of hyperaesthesia to pin-prick from D 9 to D 12. He stated that he felt as though he had an iron band round his abdomen. There was a motor paresis of the lower extremities, more marked on the right than on the left, although fixation of the right knee- and hip-joints made testing difficult. There was a loss of all forms of sensation below D 12, except for some sparing on the inner side of the right thigh and left calf, and some diminution of sensation to light touch in D 11 and D 12.

The abdominal reflexes were brisk. The knee- and ankle-jerks were not elicited, nor were the plantar responses. The bladder was distended, with a dribbling overflow, and the rectal sphincter was toneless. The prostate was normal. There was a suggestion of a kyphus at L 3 to 4, and there was tenderness over the lumbar spines. A white count showed 10,000 cells, of which 78% were neutrophils. There were no eosinophils at this time. The C.S.F. showed a normal pressure with a free rise and fall on jugular compression. The fluid was clear, contained 90 mg./100 ml. of protein, and 55 lymphocytes per c.mm.; the sugar was 46 mg./100 ml., and the Khan reaction was negative.

A further C.S.F. three weeks later showed a protein of 10 mg./100 ml., 15 lymphocytes per c.mm., and a sugar of 14 mg./100 ml. This low figure, which was checked, was not due to delay in examining the fluid.

Urine showed no protein, sugar, or abnormal cellular deposit. The test for Bence Jones proteose was negative.

X-ray examination of the spine showed marked calcification of the thoracic and abdominal aorta. There was an old crush fracture of the body of L 2 and an old anterior displacement of L 5 on the sacrum. No secondary deposits were seen.

The paraesthesiae round the abdomen gradually disappeared. The sensory level seemed to fluctuate a little, but there was virtually no alteration of sensation in the legs below L 2. The patient began to complain bitterly of shooting pains going down the legs to the knees and later to the ankles.

There appeared to be some recovery of power in the lower limbs. Six weeks after admission a muscle chart showed power ranging from 3 in the hip extensors and quadriceps to 0 in the peronei and tibialis anticus on the right side, and 0 in the flexor longus digitorum and hallucis on the left.

The illness was complicated first by a bladder infection, which was overcome, and then six weeks after admission he developed a cellulitis in the perineum followed by sloughing, and had a large ulcer in the sacral region. This was followed by spreading pressure-sores over both trochanters.

The patient's general condition deteriorated after this and his memory became poor. He slept a good deal of the day, though when questioned he complained bitterly about pains in the legs.

Attempts were made to cover the pressure-sores with pedicle grafts. The first was successful, but much bleeding occurred on the second occasion. Difficulties were experienced in the grouping of blood to transfuse him. He became very anaemic, and the grafts broke down despite eventual transfusion. His general condition, which had greatly deteriorated, did not improve; he became progressively more comatose, and died 10 months after admission.

A white count a month before death showed an eosinophilia of 21% of 13,000 cells.

Necropsy Findings

External Examination.—The body was that of an emaciated elderly male. There were extensive pressure-sores over sacrum and bony prominences of lower limbs. There was an old operation scar over the right hip and the right knee-joint was fixed and enlarged.

Internal Examination.—There was no evidence of recent injury to the vertebrae. Examination of the brain and spinal cord showed no macroscopic abnormality, and specimens were taken for histological examination. Atheroma of the cardiovascular system was moderate except in the coronary vessels, where there were some very thickened plaques, and these vessels were unduly dilated. Consolidation of the lower lobe of the left lung was present and there were some adhesions. The bladder was inflamed. All other organs appeared normal.

Histological examination of sections of the lumbar and lower thoracic cord showed giant cells and infiltration with lymphocytes and some neutrophils and many schistosome ova. The variety of schistosome was not positively identified, but one terminal-spined ovum was seen in section. Some ova appeared to have been recently deposited. There was also some degeneration of the tracts. No abnormality of the brain was seen on histological examination.

Discussion

Various diagnoses were entertained at different times. Initially the possibility of secondary deposits or myeloma of the vertebral bodies appeared possible, but the negative *x*-ray findings and lack of evidence of cord compression on lumbar puncture seemed to exclude this. The diffuse flaccid paralysis with sensory disturbance, with a suggestion in the history that the fall was a result of weakness rather than the cause of it, suggested the possibility of an ascending myeloradiculitis.

The actual diagnosis was never entertained; nothing in the history, apart from possibly his complaint of burning micturition, suggested that this patient had suffered from vesical schistosomiasis. Original routine urinary findings were normal, and the subsequent bladder infection obscured, even at biopsy, the possibility of detecting vesical schistosomiasis. The only pointer towards the possibility of bilharzia was a subsequent white count showing a fair degree of eosinophilia.

The findings at necropsy showed a rather diffuse granulomatosis of the lower dorsal and lumbar cord. In some of these granuloma schistosome eggs were visible. In Fig. 1 there would appear to be a terminal-spined ovum, and in Fig. 2 there is an ovum which is

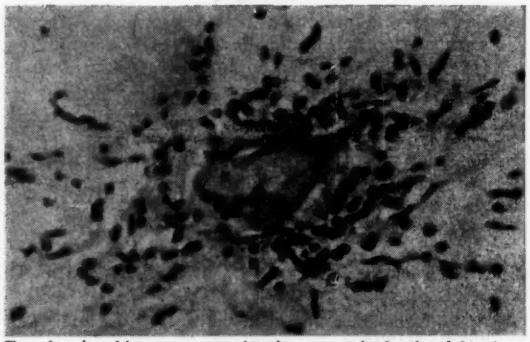

FIG. 1.—A schistosome egg showing a terminal spine lying in a granuloma in the cord.

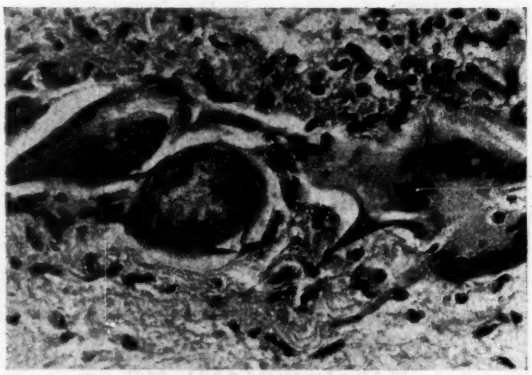

FIG. 2.—High-power view of three schistosome eggs in the cord. The spine of one is well shown.

either an *S. haematobium* broken open and the spine displaced or an *S. mansoni* egg. It was, however, not possible to identify positively whether this was an egg of *S. haematobium* or *S. mansoni*, though the appearance is perhaps a little in favour of the former. Further attempts to digest the fixed cord to identify other ova were not successful. The lesions appeared to be of very different ages, some of long standing and some comparatively recent. In addition to the granulomata there seemed to be considerable degeneration of tracts.

The ova appear to have been deposited diffusely over quite a large section of the cord. The factor determining the onset of the acute symptoms is not clear. Possibly at some point there was a critical disturbance of the cord blood supply in this region, or possibly there was a reaction of an allergic nature consequent upon the deposition of ova in the cord itself. Elaborate neurohistology was not possible, and the pathological findings do not shed further light on this.

It is not difficult to conceive how bilharzia eggs can reach the spinal canal from an infection with *S. haematobium* or *S. mansoni*.

Batson (1940) and Franks (1953) have shown that there are communications with the common iliac and inferior vena cava from the vertebral venous plexus veins. They have shown that raising the intra-abdominal pressure will cause blood from the iliac veins to pass into this system, and that this is the probable route taken by secondaries to the cord in carcinoma of the prostate.

Coman and deLong (1951) showed experimentally that they could induce tumour growth in this situation by suitable injection of a rat tumour into the iliac vein with the vena cava compressed. One of these tumours actually grew in the spinal cord.

That adult schistosomes themselves may enter the spinal canal, presumably by this route, has been demonstrated by Raper (1948).

Cases described in the literature suggest either a localized lesion with cord compression or a rather diffuse lesion as in the case described.

The one might be thought to be due to a pair of adult schistosomes ovipositing in veins in close proximity to the spinal canal, and the other as due to a rather diffuse and irregular bombardment of the cord via the vertebral venous plexus, a state that would more easily arise in *S. haematobium* infections. In fact, in view of its situation it might give rise to this complication of cord involvement more often than *S. mansoni*. That it does not do so more frequently is perhaps a little surprising. Gelfand (1950), looking for eggs, found that only one out of 25 cords of bilharzia cases showed ova, whereas they were common in the brain of these cases.

From reports in the literature there is a distinct suggestion that *S. mansoni* tends to produce a localized granuloma whereas *S. haematobium* produces a more diffuse lesion.

Diagnosis during life is not easy; schistosomiasis is widespread in many areas, yet this complication appears to be a rarity. The only cases where diagnosis has been established during life are those operated on for a suspected spinal tumour. Obrador (1948), discussing the diagnosis of cerebral cysticercosis, has mentioned that the two most helpful findings were a low sugar in the C.S.F. and an increase of eosinophils in the C.S.F. Conceivably the same condition might obtain in schistosomiasis. An increase of cells was noted in the C.S.F. of this case, but eosinophils were not specifically looked for. It was also noted that the sugar content in one specimen was unaccountably diminished.

Clearly schistosomiasis must be borne in mind when considering obscure spinal-cord lesions in those who may have been exposed to a schistosome infection at some time.

We are grateful to the Director of Medical Services, Uganda, for permission to publish this paper.

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RAPID ESTIMATION OF FIBRINOGEN IN OBSTETRIC CASES

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Patients who have had a concealed accidental haemorrhage, a death *in utero*, amniotic fluid embolism, or premature separation of the placenta are prone to severe haemorrhage associated with a defect of blood coagulation (Weiner *et al.*, 1950; Reid *et al.*, 1953). This is thought to be due to a reduction in the fibrinogen level of the blood (Dieckmann, 1936), and while theories about the causation of the defect are various (Weiner *et al.*, 1950; Albrechtsen *et al.*, 1955; Ratnoff *et al.*, 1955), the response to fibrinogen therapy has now been proved by experience (Weiner *et al.*, 1950; Reid *et al.*, 1953; Barnett and Cussen, 1954; Scott, 1955).

The clinician faced with a patient in one of these categories wishes to know as quickly as possible whether she has a deficiency of fibrinogen or whether the haemorrhage has a purely obstetric origin. A simple coagulation-time will give some information, but does not indicate anything short of a complete absence of fibrinogen and does not really enable any quantitative control of treatment to be maintained. For the most satisfactory handling of such a case a rapid estimation of the fibrinogen level is required in order that the progress of the patient may be followed and the treatment planned to meet the patient's needs. In practice it is important to decide when it is necessary to give fibrinogen and at what point in labour or the puerperium it can be used with most advantage, since it should not be administered unless really required. Of the simple methods available a straighforward coagulation-time will not always reveal the true condition of these patients, and tests which use an excess of thrombin to clot samples of whole blood (Scott, 1955) will do no more than indicate the presence of a severe defect and give no help in deciding when to intervene in the less serious cases. It is, however, of use in circumstances where it is not possible to carry out other tests.

The methods at present available for estimating fibrinogen are as follows: (1) Kjeldahl, (2) turbidimetric estimation of fibrinogen after precipitation by ammonium or other salts, (3) colorimetric estimations of fibrinogen after coagulation by thrombin or calcium salts, (4) electrophoretic methods, and (5) methods based on the addition of thrombin to varying dilutions of plasma to form a fibrin clot—for example, Rosenberg's (1956) technique.

The first four methods, though variable in their accuracy, are chemically satisfactory, but take far too long for practical use in these types of cases. The precipitation methods reviewed by Podmore (1959) can give variable results, and are dependent on such extraneous factors as the correct amount of anticoagulant being used. Methods based on clot formation by thrombin with varying dilutions of plasma—for example, Rosenberg's technique—are quick and can be calibrated to give a useful and known range of accuracy.

Some technical skill is required to make the necessary range of dilutions, and suitable reagents and tubes have to be available, but these tests are quite practical for use in emergencies.

In an endeavour to meet the need for a fast and reasonably simple method, a technique has been developed in which the minimum of equipment and technical skill is required and which uses apparatus likely to be familiar to many. In addition the fibrinogen is converted to fibrin by a substantial excess of thrombin and hence the presence of antithrombins or substances of the heparin type do not interfere. Furthermore, the reading can be made within 10 minutes and thus fibrinolysins should not substantially affect the result. In principle, plasma is clotted by thrombin in a glass cell, for use in the M.R.C. grey wedge photometer, and the optical density measured on the scale. The fibrinogen level corresponding to this will then be read from a calibration curve.

Method

The details of the method are as follows:

Apparatus: M.R.C. grey wedge photometer; No. 2 yellow-green filter; two cells for photometer; graduated pipettes for saline, thrombin, and plasma.

Solutions: Saline, 0.85% sodium chloride; thrombin, 100 units per ml. in saline prepared fresh each day.

Plasma: Centrifuge blood, preferably 5 ml. (containing 2 mg. potassium oxalate per ml.) at 2,500 r.p.m. for 5 to 10 minutes.

Procedure.—The quantities used are as follows:

	Test	Control
Saline	1.5 ml.	1.7 ml.
Thrombin	0.2 ml.	—
Plasma	0.5 ml.	0.5 ml.

First the plasma is added to the control and mixed, and then to the test solution. This should *immediately* be inverted three times before coagulation occurs, and left for 20 minutes to obtain the maximum turbidity. If required, the test can be read after 10 minutes, when about 95% of the maximum turbidity will be attained. The actual reading is taken against the control in the photometer, and the amount of fibrinogen present per 100 ml. of plasma can then be calculated from the graph (see Fig. 2).

Results

The Table shows a comparison between the results obtained by the above method and the micro-Kjeldahl estimations on the same samples. In calculating the results the readings from the grey wedge photometer have been converted to fibrinogen levels by using the calibration chart (see Fig. 2).

The Table shows the fibrinogen levels and approximate maturity of a number of pregnant patients together with the levels from a small number of normal individuals. In addition, the results obtained with plasma in which the fibrinogen has been artificially lowered are included. Most of the samples tested were collected from pregnant patients from whom blood was being taken for routine tests. However, in order to extend the range below 200 mg./100 ml., plasma was prepared with an artificial low fibrinogen content. To do this, serum and plasma were obtained from volunteers and dilutions of plasma were made in serum from the same individual. In this way varying concentrations of fibrinogen were obtained from each sample. Wherever possible, duplicate tests were carried out by separating the plasma into two portions and precipitating the fibrinogen from each quite independently, estimations being carried out entirely separately on each portion of fibrin.

As can be seen from Fig. 1, our proposed technique gives a reasonable spread of values about the mean throughout the whole of the useful range, and in Fig. 2 a proposed calibration curve is shown for this method, effective only with this type of photometer. The total time required for completing the test is 30 minutes from receiving the specimen of blood, but it can be completed within 20 minutes or less, after separation of the plasma.

Results on Bloods from Pregnant Patients, Normal Adults, and Artificially Lowered Plasmas

Pregnancy (Weeks)	Bloods from Pregnant Patients			Normal Bloods			Artificially Lowered Plasmas		
	Grey Wedge		Kjeldahl mg./100 ml.	Grey Wedge		Kjeldahl mg./100 ml.	Grey Wedge		Kjeldahl mg./100 ml.
	Optical Density	mg./100 ml. from Fig. 2		Optical Density	mg./100 ml. from Fig. 2		Optical Density	mg./100 ml. from Fig. 2	
39/40	58	475	534	48 48	375 375	381 369	24 25	135 145	150 130
	59 52	485 415	441 420	45 43	345 325	388 375	18 17	75 65	55 39
	55 53	445 425	346 320	36 35	255 245	256 244	30	195	175
	60 56	495 455	563 507	39 38	285 275	234 227	25	145	135
	47	365	408	39 36	285 255	278 234	22	115	109
	49 49	385 385	384 384	42 40	315 295	328 278	30	195	168
	48 45	375 350	360 317	36 35	255 245	229 226	23	125	104
	55	445	607	45	345	364	21 21	105 105	103 112
	50 49	395 385	399 289	42	315	358	20	95	128
35/36	53 49	425 385	474 363				26 23	155 125	203 190
	55 55	445 445	450 350				18 21	75 105	101 134
	65 64	545 535	555 506				16 17	52 65	96 82
	51 49	405 385	405 392				20	95	108
	55 51	445 405	532 518				31 28	205 175	116 115
	65 65	545 545	490 479				23	125	67
33/34	52 51	415 405	437 354				17	65	74
	56 52	455 415	360 324						
	55	445	324						
	54 46	435 355	415 401						
	39 39	285 285	402 365						
	50 49	395 385	405 405						
	55 52	445 415	539 528						
30/33	52 50	415 395	408 398						
	61 59	505 485	427 392						
26/29	42	315	245						
	64 62	535 515	536 494						
20/25	47 46	365 355	316 294						
13/18	61	505	427						
	42 39	315 285	315 208						
8/12	47 42	365 315	317 255						
	49 48	385 375	368 343						

The only important disadvantage found with this method is that haemolysed blood gives abnormally high values and so is unsuitable for this test.

Discussion

It is of little practical importance whether a patient's fibrinogen level is 200, 250, or even 300 mg./100 ml., but it is of great importance to know when it is as low as 50 mg./100 ml., and particularly whether it is rising or falling at this point. With such a simple test it is possible—assuming that the patient's veins remain patent—to take estimations at hourly or two-hourly intervals until after delivery and so obtain a series of readings, comparisons between which give a much more reliable picture of her condition than any single observation.

The ready availability of a method of estimating fibrinogen has proved of great value in enabling results to be obtained in likely cases before a failure of blood coagulation has become apparent, and in such cases prophylactic treatment can be planned as necessary, and supplies of fibrinogen and blood of the correct group obtained well in advance of delivery.

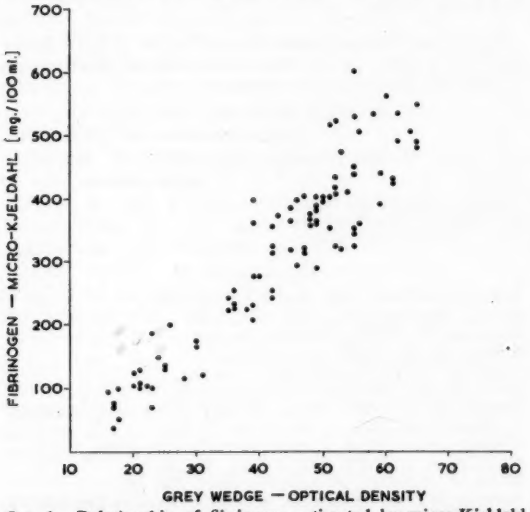

FIG. 1.—Relationship of fibrinogen estimated by micro-Kjeldahl and the optical density by the grey wedge photometer.

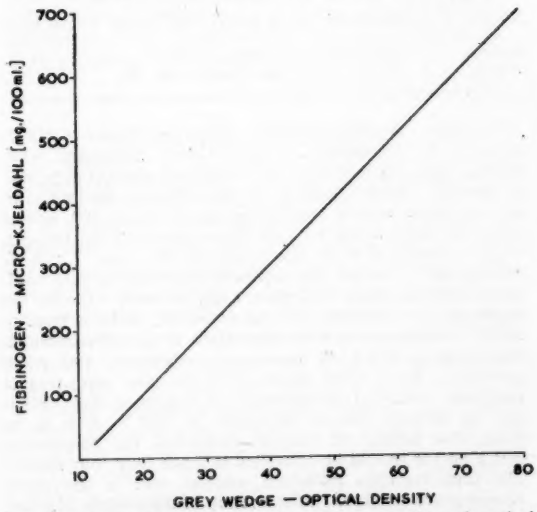

FIG. 2.—Proposed calibration chart for conversion of optical density measurement to mg./100 ml. of plasma fibrinogen.

In such a case as this the administration of fibrinogen can be held over until the patient is at or near delivery, provided that no actual haemorrhage occurs and that the fibrinogen level remains around 100 mg./100 ml. If it falls below 50 mg./100 ml. the administration of fibrinogen is probably wise. Even so, it is desirable to follow the progress of the fibrinogen level in order to see whether the infused fibrinogen is being destroyed or not.

Summary

The need for a rapid method of estimating fibrinogen in cases of hypofibrinogenaemia and the value of serial estimations are discussed.

A method of measuring directly the density of fibrin produced by adding thrombin to plasma is proposed and a calibration chart for the M.R.C. grey wedge photometer is given.

We thank Dr. John Murray, the director of research, for encouragement and advice throughout, and the numerous doctors, nurses, and colleagues of Queen Charlotte's Maternity Hospital who have helped with the collection of specimens.

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Medical Memoranda

Two Unusual Complications of Umbilical Hernia in Childhood

It is now generally accepted that the condition of infantile umbilical hernia is a harmless one with a strong tendency to self-cure. Both incarceration and rupture of such herniae are extremely uncommon, and they rarely give rise to any symptoms. Though in no way affecting the accepted principles of management for this type of hernia, we feel that the following two cases, one of strangulation of omentum and the other of spontaneous rupture, are worth recording.

CASE 1

A girl of 7 years was noticed in infancy to have a small umbilical hernia. Early in her fourth year she was seen in this department when the hernia was small and easily reducible, and treatment was not thought to be necessary. She was seen again in her seventh year after several attacks of acute central abdominal pain. The hernia was still present, and would admit the tip of a little finger. It was felt that the attacks of pain were unrelated to her hernia.

Almost a year later, after a sharp bout of coughing, she complained suddenly of severe central abdominal pain. During the afternoon she lay on a sofa in continuous pain,

made worse by coughing or movement, and severe enough at times to make her cry. In the early evening, when put to bed, she was found to have a tender black swelling, the size of a grape, at the umbilicus. During the next two days the pain gradually became less severe and the swelling diminished a little in size. She had some nausea and loss of appetite, but her bowels were acting normally.

When admitted to hospital on the third day she still had pain, made worse on an attempt to walk or by any jerky movement. The swelling at the umbilicus, dark blue in colour, measured just over a centimetre in diameter and was extremely tender. The umbilical scar formed the crown of the swelling, and the skin, though a little stretched, was normal in appearance.

After two days in hospital the swelling had decreased very little in size, and at operation she was found to have a true infantile umbilical hernia containing a knuckle of strangulated omentum adherent to the hernial sac. Omentum and sac were excised, the hernia was repaired, and the child made an uneventful recovery.

CASE 2

A female infant aged 1 year had been admitted to hospital one month previously for the removal of supernumerary digits. She was then found to have an easily reducible infantile umbilical hernia 1 in. (2.5 cm.) in diameter. Her mother thought this had been present since birth, but it had not given rise to any trouble.

Three weeks after her discharge the child was readmitted as an emergency case, because her mother had noticed a small tag of tissue protruding from the umbilicus. When she bathed the child at 10 a.m. the hernia appeared quite normal: at 12.45 p.m., when changing the infant's napkin, she noticed a piece of red fleshy material protruding from the umbilicus. The infant was brought straight to hospital, and was there found to have a small triangular piece of omentum protruding through apparently normal skin at the apex of the hernia. The surrounding tissues appeared normal, and there was no evidence of infection or necrosis.

Careful inquiry failed to elicit any cause for the rupture; in particular, there was no suggestion of trauma by the napkin-pin. The child had a slight cough at the time, but there was no history of a paroxysm or of sustained crying.

A Mayo repair of the umbilical hernia was carried out, and the prolapsed omentum excised. The infant made an uneventful recovery.

COMMENT

Browne (1952) was unable to find any record of a strangulated umbilical hernia in childhood. Miller (1932) reviewed all cases of umbilical hernia admitted to Massachusetts General Hospital in a 20-year period; his discussion was concerned with the problem in adults, but a table showing the age and sex distribution of strangulation included one patient aged 2 years. Crump (1952), describing a series of 329 cases of umbilical hernia in American negro children, mentioned a case of strangulation in a 17-months-old girl but gave no clinical details. Woods (1953) mentioned the case of a child 2½ years in whom a sudden protrusion at the umbilicus was accompanied by pain and vomiting, and the tender mass found there was presumed to be a small portion of omentum nipped in the orifice. Operation relieved the symptoms and signs, but the hernia was anatomically the so-called adult type of oblique hernia mentioned by Browne (1952).

Haworth (1957) reported two cases of strangulation. In the first, a 4-year-old boy with nephrotic syndrome, the picture was complicated by ascites, and in the second, a 5-months-old boy with an umbilical and a right inguinal hernia, the bowel and omentum were viable at operation.

Nine cases of spontaneous rupture of an umbilical hernia were found in the literature, five of these in children. Von Arnold (1860) reported the spontaneous rupture of an umbilical hernia in a child of 4 years. Extrusion of intestine occurred through the wide umbilical ring and the child died. Porcher (1883) gives an account of a negro girl aged 13 years with spontaneous rupture, extrusion of omentum, and recovery after operation. MacLean (1950) records spontaneous rupture in a 3-months-old infant after a bout of crying, and Ninh and Hoanh (1951) reported a similar case in a malnourished infant of 20 days. Strange (1956) recorded a spontaneous rupture in a Chinese child of 3 months, with death on the third day after operation.

The only comparable case seen in this department in the past 15 years was that of a 2-months-old infant in whom gross abdominal distension led to rupture with protrusion of the intestines in the course of a general peritonitis of unknown aetiology.

The rarity of serious complications gives additional support to the present policy of withholding surgery and awaiting natural cure of umbilical hernia during the first five years of life.

Case 1 was admitted under the care of Dr. F. J. W. Miller and Case 2 under Dr. G. Davison, to both of whom we are grateful for permission to publish.

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"Though, in itself, *Modern American Cookery* (1837) represented a fascinating example of early Americana, what made it particularly interesting to me, as a medical man, was its subtitle, 'With a List of Family Medical Recipes.' In the one short section comprising pages 181 to 199, one is given the opportunity to view American medicine through a lay person's eyes in the pre-Civil War era. . . . It is informative to review the attitudes expressed in this book and to compare them with present day attitudes. To-day the statement is often made that the American public is treating itself indiscriminately with medication to an unprecedented degree as a result of newspaper, television, and radio publicity. It is often stated that the awe and respect previously accorded the physician is lacking to-day. What was the attitude toward physicians in 1837? It is to be noted that among 43 illnesses described, the admonition that a doctor should be consulted is made only four times! The four maladies in which medical care is considered advisable are smallpox, inflammation of the bowels, bleeding at the nose, and gravel!" (Dr. Walter Lentino in *J. Amer. med. Ass.*, November 19, 1960.)

Reviews

ANTIBIOTICS IN PRACTICE

The Clinical Application of Antibiotics. By M. E. Florey, M.D. Volume IV: *Erythromycin and Other Antibiotics.* (Pp. 303+viii; illustrated. 84s.) London, New York, Toronto: Oxford University Press. 1960.

Once again we are indebted to Lady Florey for an encyclopaedic work on the clinical application of antibiotics. This volume, the third in the series (volume II, which is to be devoted to the treatment of tuberculosis, has not yet been published), deals with the erythromycin group, some of the new antistaphylococcal antibiotics, a miscellaneous group mainly suitable for local application, and antibiotics active against protozoa, fungi, and neoplastic cells. It concludes with a section on "The Choice of an Antibiotic," which summarizes much of the information in all three volumes.

The book is well documented and contains more than a thousand references, for which alone it will be invaluable to all serious students of the subject. The book is not easy to read, partly because of the mass of information, but long paragraphs sometimes covering more than two pages and often containing unrelated material do not help. It is, however, easy to criticize a book of this nature, and Lady Florey is to be congratulated on her industry. To have collected together in three volumes so much material on the clinical aspects of antibacterial antibiotics, from penicillin to ristocetin, together with notes on antifungal and antineoplastic antibiotics, is no mean task.

Few would have had the courage to contemplate such a task, both because of the work involved and because in the words of Professor Garrod "no development in medicine has ever been at once so rapid and so complex," so that books about it are liable to be out of date before publication. Lady Florey was neither daunted by, nor blind to, this fact, and on the last page she writes: "The foregoing pages have accomplished little if they have not led the reader to conclude that the value of antibiotic therapy is in a continual state of flux." This is indeed true, but the material collected together by Lady Florey will remain valuable for many years to come.

MARY BARBER.

NEONATAL PHYSIOLOGY

The Physiology of the Newborn Infant. By Clement A. Smith, M.D. Third edition. (Pp. 497+xii; illustrated. 95s.) Oxford: Blackwell Scientific Publications. 1959.

World research in medicine in all its branches has progressed at a faster rate in the fifteen years since the end of the second world war than in any other similar period of world history. In 1945 the first edition of this book was published. Since then it has been amplified to present these developments, and Dr. Smith has wisely accepted the compulsion of this development and invited colleagues in America and abroad to co-operate by criticizing certain chapters. In Great Britain, Dr. Geoffrey Dawes has looked over the sections on the circulatory system and neonatal respiration; Professor R. A. McCance and Miss Elsie Widdowson those on the foetal and neonatal nutrition, minerals, vitamins, and renal physiology. Professor Vahlquist, of Stockholm, has passed the chapter on immunology, and Dr. Smith in Boston has been guided biochemically by Dr. Claude A. Villee in the same department.

Without doubt the author has summarized very efficiently all, or almost all, relevant new work on the physiology not only of the newborn infant but on foetal and neonatal physiology of any animal in so far as it has an influence upon the human newborn infant. It is therefore a useful book of reference for the young paediatrician or experimenter working in this field, and will bring him up to date in regard to the new work and the literature.

A. ST. G. HUGGETT.

BASIC CIRCULATORY INFORMATION

Handbook of Circulation. Analysis and compilation by Philip L. Altman. Edited by Dorothy S. Dittmer and Rudolph M. Grebe. (Pp. 393+xv. 52s.) Philadelphia and London: W. B. Saunders Company. 1959.

This handbook weighs 2¼ lb. and measures about 11 by 8½ by 1 inches. It consists of a mass of tables, and long lists of references often occupy the lower half of a page. These references are set out in prose form and are not in alphabetical order; nor are the titles of the papers given. Obviously, then, this is not the sort of handbook you can carry around in your pocket or refer to very easily. However, it was supposed that these unprepossessing qualities would be offset by the excellence of the tables. But how is one to judge the excellence or otherwise of 363 pages of tables in small print? Before passing the book on for someone else to review, it seemed fair to test its value and accuracy by looking up specific items in the index. I started with acetylcholine: the index referred me to p. 278—"effect on hearts (insects)." I turned to morphine: there were two pages listed, one concerning the effect of morphine on insects (p. 280), and the other on its cardiovascular action (p. 250). In the table on p. 250 the reference to morphine is "sedative for acute myocardial infarction or acute congestive failure."

Switching to physiology, I looked up cor pulmonale (p. 332). Here the page was devoted to demonstrating a close correlation between the arterial oxygen saturation and the pulmonary artery pressure. Rather desperately I turned to pulse configurations in man (p. 156). On this page is the left atrial configuration in mitral stenosis. The tracings show a *y* descent barely dissimilar to the speed of other *y* descents in other tracings from different conditions shown on the same page, and a return of pressure from the *y* nadir before the next *a* wave. Shocked, I glanced at the next page and saw a tracing depicting the anacrotic pulse with the anacrotic notch almost as high as the tidal wave. On this page there was also a pulsus bisferiens, which looks practically the same, except that there is a faster initial ascent. What sort of handbook is this, put out by the National Academy of Sciences, National Research Council, U.S.A.?

Clearly it is as likely to mislead as to guide the clinician, and it would appear to be of little value to research workers concerned with problems relating to clinical cardiology. The foreword suggested it might be much more basic. Refreshed with this idea I tried the output test. This law states that the sum of all systemic territorial blood flows should equal the cardiac output. The handbook evaded the test by failing to give the majority of the territorial blood flows. Precise information on cerebral, renal, and hepatic blood flows, however, was well presented. Encouraged, I looked up

the relative ventricular weights during the first three months of life, data not at all easy to obtain, and there on p. 22 was exactly the information I had been seeking. Delighted, I tried a few haemodynamic formulae, and these were quickly found, nicely set out together on pp. 355–6.

And so the lesson went on: the more basic the information required, the more likely was it to be found and the more accurate were the data. And that is both the secret and the value of this handbook. The amount of work that must have gone into its production is prodigious and there can be nothing quite like it in cardiovascular literature.

PAUL WOOD.

QUANTITATIVE BIOLOGY

Carcinogenesis by Ultraviolet Light. An Essay in Quantitative Biology. By Harold F. Blum. (Pp. 340+xv; illustrated. 52s.) Princeton, N.J.: University Press. London: Oxford University Press. 1959.

Radiation in the near ultra-violet region around 250 mμ to 320 mμ is carcinogenic, and it has provided the research worker with a particularly fine tool for the examination of the carcinogenic process. It has yielded data which are reasonably complete and analysable, and which merit very serious consideration compared with the more meagre data to be obtained by employing other carcinogenic agents. The experiments on the ultra-violet induction of cancer do not support some current concepts of the carcinogenic process but do lead to conclusions which can be used to challenge these concepts and to suggest further experimental work. These are the main contentions of this book, and they are well supported and clearly discussed.

Ultra-violet carcinogenesis is a fascinating topic, and this summary of the work in the field should interest a wide variety of readers. Realizing the need to carry physicists, chemists, and biologists with him in his discussion, the author, in the first half of his book, defines basic terms and describes the varied effects of ultra-violet and visible radiation on biological systems. The inactivation of enzymes and viruses, haemolysis, lysogenicity, photodynamic action, and examples of the photo-recovery which sometimes results from exposure to visible after ultra-violet radiation, are mentioned in sufficient detail to point probable differences between the mechanisms of these effects. This provides a useful background for the discussion of ultra-violet carcinogenesis. Much of the work in this field has been carried out by the author and his collaborators, and it is good to have the results collected and reviewed in one volume. The animal data are extensive, and gathered from experiments which are beautifully designed and executed. From these are drawn the conclusions about the process of cancer induction by ultra-violet radiation which are extended later to other carcinogens, and which make this book of quite general importance in the cancer field. Dr. Blum finds that carcinogenesis is a continuous process which cannot be separated into distinct periods; that it is cumulative; and that it is essentially irreversible. Evidence for some small degree of recovery is seen in the failure of reciprocity at very low dose-rates; but the threshold at which recovery just balances cancerization is very low and not directly measurable. So, in a practical sense, ultra-violet carcinogenesis is non-threshold. Further, comparison of tumour growth-rate curves with models indicates that, during regularly repeated dosage, the tumour grows by the proliferation of an increasing number of clones, the proliferation rate of all these clones being constantly accelerated.

At this point speculation commences as to the basic replicating unit which governs the growth of a tumour. The "tem" is introduced. This is neither a virus, nor a mutated gene, nor an intermediate chemical formed by the ultra-violet radiation, but a high-molecular-weight template which is not readily diffusible; it could be a polynucleotide. The speculations are by no means far-fetched, and perhaps gain some support from recent work on the induction of animal tumours by injection of nucleic acids.

The section on sunlight and human skin cancer is brief, but this is not the author's own experimental field, and its data, in any event, are far less clear-cut. One of the merits of this book is that it should stimulate the collection and assist the analysis of more of these data. A final word on public attitudes to environmental cancer hazards arises quite naturally from the conclusions as to the carcinogenic process.

This book summarizes a complex problem clearly and logically, and its conversational style and lay-out make it easily read. It is, indeed, "an essay in quantitative biology," and as such it will repay study by all cancer workers.

E. M. F. ROE.

FOSTER CARE

In Place of Parents. A Study of Foster Care. By Gordon Trasler, Ph.D. (Pp. 248+viii. 25s.) London: Routledge and Kegan Paul. New York: Humanities Press. 1960.

There are 61,000 children in the care of local authorities and voluntary organizations in England and Wales of whom 47% are boarded out in foster homes. Between one-third and two-fifths of foster-home placements "fail" for one reason or another. In spite of (or perhaps because of) years of vigorous discussion about the factors associated with success or failure in this kind of care, little research has been carried out. Dr. Trasler's illuminating study of 57 children who were boarded out unsuccessfully at least once, in the County of Devon, and of a "contrast group" of 81 successful placements, does much to get us thinking about how such research can be done.

The book is in two parts: the first is a qualitative account, illustrated with much case-history material, of important determinants of failure of boarding out; the second part presents statistical findings. In his discussion of the dynamics of the foster-home situation Dr. Trasler shows himself aware of the many factors that contribute to its quality. "It is not easy," he says, "to be a good parent to one's own children, but it is much more difficult to be a good foster parent." He goes on to show why this should be so. The statistical findings are full of interest. Separation from the mother at an early age was not more common among the study sample of foster-home failures than among the contrast group of successful placements; but the total amount of institutional care during the first three years of life was very significantly related to subsequent failure. Aggressive children more commonly had a longer institutional history. Two-thirds of those children who were placed in foster homes before they were 4 years old achieved a good adjustment, whereas of children placed between 7 and 13 years only 30% did. Women over 40 years of age were more often successful as foster mothers than were younger women. There was evidence

that the presence in the home of a foster parent's child of the same sex and about the same age was associated with a higher failure rate. These and other findings are intelligently discussed and placed in their context.

As the author points out, the book is something of a pilot study. As such it fulfils its purpose excellently. It is to be hoped that other studies, replicating and extending his findings, will be carried out in other parts of the country, and that the merits and drawbacks not only of fostering but of other forms of care will be more widely scrutinized.

J. TIZARD.

EXPLAINING TO THE PATIENT

That the Patient May Know. An Atlas For Use by the Physician in Explaining to the Patient. By Harry F. Dowling, M.D., Sc.D., Tom Jones, B.F.A., assisted by Virginia Samter. (Pp. 139+xiii; illustrated. 52s. 6d.) London, Philadelphia: W. B. Saunders Company. 1959.

This is a book of large-scale diagrams, boldly done in black and red and interspersed with textual explanation in the same style, intended to help the doctor to explain to the patient what is wrong, mechanically or physiologically, and, sometimes, the rationale of treatment. Some pages are given to food values, their fat and salt contents and exchange quantities; there are diagrammatic accounts of the anatomy and physiology of the main systems, illustrations of the main changes in some common diseases and of the anatomy of pregnancy and childbirth. Self-administration of insulin is illustrated and so is the relative expenditure of energy in various common activities. The preface emphasizes that the book is meant to be in the hands of the doctor for exposition to the patient and is not intended for lay reading.

Probably every doctor accustomed to explain things to patients would be glad of one or other of these diagrams from time to time—to explain, for example, a "slipped disk" or a fracture—but for the most part only a patient familiar with medical diagrams and not easily perplexed or scared would seem likely to receive precisely the impression the doctor wished to convey, and it would be hard to be sure he *had* received it. The aim of the book is commendable, but it might have been better to limit its range to subjects which lend themselves to explanation by diagram. Some of those here illustrated do not.

L. W. BATTEN.

PHOTOGRAPHY IN MEDICINE

Photography in Medicine. By Arthur Smialowski and Donald J. Currie M.D., M.Sc., F.R.C.S.E., F.R.C.S.(C.), D.S., F.A.C.S. (Pp. 330+xviii; illustrated. £5 16s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

This is a refreshingly new book from Canada and should undoubtedly be included in the top five titles on the subject: this is not to imply that other literature is abundant. Twin authorship by the head of a hospital photographic department and an enthusiastic clinician seems in this instance to be a successful formula and has resulted in a well-balanced view. Above all else this is a comprehensive work and deals in adequate detail with all aspects of medical photography from the department itself, through special techniques and requirements in the various branches of medicine, to filing and indexing of finished material. This latter section at least might be criticized for being unrealistically cumbersome in relation to a 10 or 20% recall requirement. There is also a brief section on photography in the consulting-room which, though ambitious in its concept, overlooks many of the simple kits which are available to the doctor-photographer.

Some of the good ideas contained in this book may be a little immature and divorced from practice—for example, scaffolding over the operating-theatre table, though considered utopian by many of us, has obvious practical limitations. In a similar way it is difficult to see some of the "custom built" endoscopic cameras being developed for general use. To these and a few other notions the term "imagineering" might be applicable. The brief entry on retinal photography—admittedly a specialist subject—does not incorporate the most recent advances in this sphere. Happily we no longer have to depend on the stalwart Zeiss-Nordenson camera or the Bausch and Lomb copy. The number of new models now being distributed in Europe makes it probable that there are more retinal cameras outside medical photographic departments than inside; hence more comprehensive technical guidance would be welcomed by many non-specialists.

From the publishing standpoint this is an expensive and unnecessarily lavish production. This criticism is based first on the large number of full-page illustrations which would have suffered nothing by reduction in size, and secondly on the choice of such a large type-face generously leaded. This aspect is not the concern of the authors beyond the undeniable fact that the market is small and the production cost has put the book outside the individual purchasing power of technical staff who would really benefit from this otherwise excellent treatise.

PETER HANSELL.

MANIPULATIVE TECHNIQUE

Les Manipulations Vertébrales. By Robert Maigne. Preface by Professor de Sèze. (Pp. 246; illustrated. NF. 28.) Paris: Expansion Scientifique Française. 1960.

A minor disk-lesion with displacement susceptible of manipulative reduction is a commonplace. Unhappily, as we all know, nearly all spinal manipulation is to-day carried out by laymen, styling themselves bonesetters, osteopaths, or chiropractors. However, doctors are beginning to deplore the hiatus in medical education that forces patients to go outside the medical profession for what is clearly medical treatment. It is a welcome sign of awareness of this problem that two books have recently appeared describing osteopathic method: Stoddard's in England and Maigne's in France. Both these authors are medical men practising osteopathy, and all doctors should be grateful to them for putting their knowledge at our disposal.

Maigne's book largely restricts itself to the spinal joints, with small sub-sections on coccygodynia, tennis-elbow (most misleading), and strain of the costovertebral joints. There is also a chapter on exercises by Waghemacker with 32 photographs. Many of these exercises are intended to increase spinal mobility towards flexion, and would not often be used after spinal manipulation in this country. The main part of the book is devoted to manipulative technique at the joints from atlas to sacro-iliac. The text is explanatory, aided by diagrams and 200 clear photographs. As a manual for those medical men who wish to manipulate in the same way as osteopaths do, this account could hardly be bettered.

However, books on osteopathy are a mixed blessing to the would-be medical manipulator. Osteopaths manipulate without adequate traction, thus losing the advantage of a strong centripetal force acting on the articular contents. In consequence they are driven to adopt a welter of complicated manœuvres, when much simpler measures carried out during traction would have sufficed. For example, Maigne needs no fewer than 58 photographs and diagrams to demonstrate the different ways of moving the cervical joints.

The other disadvantage of books based on osteopathy is the vague way the clinical examination is conducted. Some spinal movements are tested, tender points are palpated—and the manipulator is all set. It seems to me that osteopaths, even when medically qualified, cast their net far too wide. It is not enough to find limited movement at a spinal joint; the relevance of this finding to the patient's complaint needs to be established. This book includes a tendentious section by Lescure on the possible visceral effects of manipulation. He does not consider the view that, when "coronary thrombosis" or a "grumbling appendix" is relieved by manipulation, he is dealing with misdiagnosis, and that in fact a root-pain caused by a thoracic disk-lesion has been relieved. This book, then, can be commended as an atlas of manipulative technique, but will command little agreement on its theoretical or clinical aspect.

JAMES CYRIAX.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Hospital Infection. Causes and Prevention. By R. E. O. Williams, M.D., M.R.C.P., R. Blowers, M.D., L. P. Garrod, M.D., F.R.C.P., and R. A. Shooter, M.D. (Pp. 307+x; illustrated. 35s.) London: Lloyd-Luke (Medical Books) Ltd. 1960.

Carcinoma in Situ of the Uterine Cervix. A Study of 235 Cases from the Free Hospital for Women. By Gilbert H. Friedell, M.D., Arthur T. Hertig, M.D., and Paul A. Younge, M.D. (Pp. 154+viii; illustrated. 60s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1960.

Pseudomonas Aeruginosa Infections. By Claude E. Forkner, Jr., M.D. (Pp. 104+vi; illustrated. $5.25.) New York and London: Grune and Stratton. 1960.

Segundas Jornadas Venezolanas de Gastroenterologia y Nutricion 14, 15, 16 de julio de 1955. Colegio Medico del Distrito Federal. Organizadas por la "Sociedad Venezolana de Gastroenterologia, Endocrinologia y Nutricion" en su Decimo Aniversario 1945-1955. (Pp. 618; illustrated. No price.) Caracas: Prensa Medica Venezolana. 1956.

Klinische Chirurgie für die Praxis. Vol. III. Edited by O. Diebold, H. Junghanns, and L. Zukschwerdt. (Pp. 210; illustrated. DM. 40) Stuttgart: Georg Thieme Verlag. 1960.

Health and Hormones. By A. Stuart Mason. (Pp. 200; illustrated. 4s.) London: Penguin Books. 1960.

The Care of Invalid and Crippled Children. Edited by A. White Franklin, M.B., F.R.C.P. With a Foreword by Letitia Fairfield, C.B.E., M.D., D.P.H. (Pp. 158+xiii. 8s. 6d.) London, New York, Toronto: Oxford University Press. 1960.

The Compleat Imbiber. Edited by Cyril Ray. Illustrations by Brian Keogh. (Pp. 175; illustrated. 25s.) London: Putnam and Co. Ltd. 1960.

Ultrafiltration. By L. Ambard, M.D., and S. Trautmann. With a Preface by A. M. Monnier. (Pp. 67+x; illustrated. 36s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications Ltd. 1960.

The Proceedings of the Diamond Jubilee International Clean Air Conference. London, 20-23 October 1959. (Pp. 290; illustrated. 30s.) London: National Society for Clean Air. 1960.

Clinical Child Psychiatry. By Kenneth Soddy, M.D., D.P.M. (Pp. 470+x. 42s.) London: Baillière, Tindall and Cox. 1960.

Fundamentals of Psychology. By C. J. Adcock, M.A., Ph.D., Dip.Soc.Sci., F.B.Ps.S. (Pp. 220; illustrated. 12s. 6d.) London: Methuen and Co. Ltd. 1960.

Atlas der Gynäkologischen Anatomie. By Heinrich Martius and Käthe Droysen. (Pp. 118+viii; illustrated. DM. 49.) Stuttgart: Georg Thieme Verlag. 1960.

Teach Yourself Atomic Physics. By J. M. Valentine, B.Sc., Ph.D., F.Inst.P. (Pp. 192; illustrated. 7s. 6d.) London: The English Universities Press Ltd. 1960.

Il Cancro dell'Utero dalla Macroscopia all'Ultrastruttura. By Carlo Sirtori and Ettore Morano. (Pp. 268; illustrated. No price.) Milan: Casa Editrice Ambrosiana. 1960.

L'Infection Staphylococcique. By Robert Worms. (Pp. 443. NF. 55.) Paris: Editions Médicales Flammarion.

Uprooting and Resettlement. (Papers presented at the 11th Annual Meeting, Vienna, August, 1958, of the World Federation for Mental Health.) (Pp. 150. 10s.) London and New York: H. K. Lewis and Company Ltd. 1960.

A Dictionary of Scientific Terms. Pronunciation, Derivation, and Definition of Terms in Biology, Botany, Zoology, Anatomy, Cytology, Genetics, Embryology, Physiology. By I. F. Henderson, M.A., and W. D. Henderson, M.A., B.Sc., Ph.D., F.R.S.E. Seventh edition by J. H. Kenneth, M.A., Ph.D., F.R.S.E., F.R.S.G.S. (Pp. 595+xv. 32s.) Edinburgh and London: Oliver and Boyd. 1960.

Die Künstliche Hibernation. By Professor Dr. med. P. Veghelyi in collaboration with R. Pertorini, L. Palos, and G. Ruzicska. Second edition. (Pp. 611; illustrated. No price.) Budapest: Akademiai Kiado. 1960.

Enzymologie der Geburtshilfe. (Normale und pathologische Gestation im Licht von Serumfermentuntersuchungen.) By Doz. Dr. med. habil. Erwin Rimbach. (Pp. 116+x; illustrated. DM. 17.) Jena: Veb Gustav Fischer Verlag. 1960.

Cancer. The Significance of Delay. By Robert Sutherland, M.D., D.P.H. (Pp. 206+ix+7. 30s.) London: Butterworth and Co. (Publishers) Ltd. 1960.

Referátovy Vyber Z Tuberkulosy a Pneumologie. Editor: Mudr. Erich Jancik. (Pp. 240+iv. No price.) Prague: Ustav Pro Zdravotnickou Dokumentaci. 1960.

Space Biology. The Human Factors in Space Flight. By James Stephen Hanrahan and David Bushnell. (Pp. 263+vi; illustrated. 35s.) London: Thames and Hudson. 1960.

Phosphorus Metabolism of Brain. By P. J. Heald, M.Sc., Ph.D. (Pp. 195+vii. 42s.) Oxford, London, New York, and Paris: Pergamon Press. 1960.

Chemicals in Food and in Farm Produce: Their Harmful Effects. By Franklin Bicknell, D.M.(Oxon.). (Pp. 192. 12s. 6d.) London: Faber and Faber. 1960.

The Adrenal Circulation. By R. G. Harrison, M.A., D.M., and M. J. Hoey, B.Sc. (Pp. 77+vii; illustrated. 25s.) Oxford: Blackwell Scientific Publications Ltd. 1960.

Atlas of Systematic Human Anatomy. By G. Wolf-Heidegger, M.D., Ph.D. Volume I. Second edition. (Pp. 223; illustrated. Sw. Fr. 35.) Basel and New York: S. Karger. 1961.

Medicina Neotropical. Tripanosomiasis Americana. (Pp. 203+v; illustrated. No price.) Caracas: Laboratorio Behrens. 1960.

Bulletin de l'Institut de Médecine Experimentale. Volume III. (Pp. 275; illustrated. No price.) Bulgaria: Edition de l'Académie des Sciences de Bulgarie. 1960.

Chromatographic and Electrophoretic Techniques. Volume I. ***Chromatography.*** Edited by Ivor Smith, B.Sc., Ph.D., F.R.I.C. (Pp. 617+xvii; illustrated. 65s.) London: William Heinemann Ltd. 1960.

Chromatographic and Electrophoretic Techniques. Volume II. ***Zone Electrophoresis.*** Edited by Ivor Smith, B.Sc., Ph.D., F.R.I.C. (Pp. 215+viii; illustrated. 30s.) London: William Heinemann Ltd. 1960.

Surgery for Nurses. By James Moroney, M.B., Ch.B., F.R.C.S.(Eng.), L.R.C.P.(Lond.). With a Foreword by Miss Dorothy M. Smith, O.B.E. Seventh edition. (Pp. 792+xii; illustrated. 32s. 6d.) Edinburgh and London: E. and S. Livingstone Ltd. 1961.

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BURSTING AT THE SEAMS

In 1958 the population of the world was estimated to have reached 2,854 million[1] and to be increasing at an average rate of 1.7% each year. It will therefore pass 3,000 million in 1961. The present world birth rate of 35 per thousand adds some 100 million babies to the population every year, while the estimated death rate of 18 per thousand subtracts 51 million, leaving a net annual gain of something over 48 million inhabitants—more than the whole population of England and Wales. The rate of increase is greater in those underdeveloped parts of the world where the level of living is very low. The highest regional rates of natural increase are those for Central America (2.7% per year), South-west Asia (2.5), South America (2.3), Oceania (2.3), South-east Asia (2.1), and Northern Africa (2.0); the lowest rates are for Northern and Western Europe (0.6), Central Europe (0.8), and Southern Europe (0.9).

Even in the relatively short run to 1975 the population of the world is expected (on moderate assumptions) to rise by about one-third of the existing total to 3,830 million.[2] Asia, which already contributes more than half the population of the world (1,591 million) will increase its share and will then have a population of 2,210 million, almost as large as was the population of the whole world at about 1950. In this monsoon region there are already high concentrations of people and a level of living desperately low by any standards; and there can be no early relief from the pressure of numbers. Latin America will increase its population by one-quarter to 240 million, and Africa will increase its numbers from 231 to 303 million. In large parts of these areas there is ample living space, but full exploitation of potential resources is retarded by lack of capital and by social and cultural obstacles to the effective deployment of existing or of much-needed immigrant manpower. The population of the Soviet Union is expected to increase from 209 to 275 million. Here too there is still adequate space for expansion. The population of North America will, by 1975, increase from 193 to 303 million and that of Europe from 420 to 476 million. The moderate increase in Europe is in sharp contrast to the massive growth in population elsewhere. By 2000, if nothing happens to change the trend, the position may be far worse. The world population will then be 6,230 million and Asia will hold 3,870 million, two-thirds of the population of the world. Europe without the Soviet Union will have a mere 568 million.

It is only 15 years ahead to 1975, and in this period the pace at which the world population grows is expected to quicken unless some much greater effort than has yet been seen is made to resist it. Should it be resisted? Those who think not pin their faith on the possibilities of expanding food production and on the discovery of additional resources: these potentialities, they claim, are almost limitless. On whether there will be room to live as well as food to eat, and on what is to happen to those at present starving, they are less assured. Those who counsel resistance are concerned at the way in which the world's food production is not keeping pace with its population growth. There is a middle view that population growth will slow up in response to industrialization, and that everything should therefore be done to accelerate economic development and to eliminate existing impediments to international trade.

Medicine cannot turn aside from this problem. By far the greatest factor accelerating the growth of population in the underdeveloped areas has been the decline in mortality as a result of widespread campaigns against disease, especially malaria, and of intervention, medical and economic, largely by the developed countries. But those influences tending to reduce fertility in the economically well-developed areas have not yet penetrated to the poorer areas, so that birth rates have fallen only slightly, if at all. Disease stalks in the shadow of their poverty, and medical hopes of improving health and vitality are apt to be frustrated there. The richer countries, which are growing relatively richer, clearly have a special responsibility to help the poorer countries to escape the danger of adding greatly to their populations before they possess the means to support them.

[1] *Demographic Yearbook 1959*, 1960. U.N. Statistical Office.
[2] *The Future Growth of World Population*, 1958. U.N. Department of Economic and Social Affairs.

TESTS FOR CARCINOGENIC ACTIVITY IN FOOD

The causes of most of the common forms of cancer in man remain undiscovered, but in a few instances —skin and bladder—chemical substances foreign to the body have been incriminated, while chemicals in tobacco smoke are strongly suspected to be one cause of cancer of the bronchus. As a result of intensive laboratory work, many chemicals have been shown to be capable of producing tumours in

experimental animals. There is naturally some anxiety that carcinogenic materials may inadvertently be added to man's environment as a result of technological advances, and those faced with the responsibility of demonstrating the harmlessness of the food products they wish to sell ask what type of test should be carried out. Two publications on this question have recently appeared, one from the National Academy of Sciences, Washington,[1] and a much shorter report from the Ministry of Health.[2]

The American publication gives a well-documented account of the whole problem of chemical carcinogenesis and the use of animals in evaluating such hazards to man. The British report only summarizes current opinion. Both documents outline the type of test they think is adequate. This is intended to give the manufacturer some idea of the scale on which he will have to finance experimental work to test his product. The British report points out the undesirability of prescribing a set pattern of tests to which everyone should conform, and emphasizes that, wherever appropriate, past experience should provide the basis for deciding on tests for a new compound. This view finds support in data given in the U.S. report. Thus, of 450 compounds shown to be carcinogenic, over 200 are polycyclic hydrocarbons, 50 are azo-dyes, and many others aromatic amines and carbamates. Obviously the tests found satisfactory for these should be used to examine a new substance belonging to one of those chemical groups. Where no guide is provided by existing knowledge, the British report calls for the material to be given to rats and mice both by mouth and by repeated injections for the life span of the animals. The Americans recommend the feeding of rats and dogs (the latter for four years) and repeated applications to the skin of mice. The U.S. experts disagree with their British counterparts on the value of repeated injections in testing food additives. The Americans point to the well-known fact that many substances such as glucose and salt, if injected in strong solutions, can give rise to malignant tumours in the subcutaneous tissues of the rat. This is recognized in the Ministry's report by a caution that "parenteral tests [injections] by themselves will not provide evidence on which any decision about the safety of the test material can be based." It seems questionable whether such tests are suitable for food additives if they give results of such dubious significance. The Americans limit themselves to a single injection or implantation into mice.

The value of topical application to the skin of mice is undoubted in the testing of such materials as polycyclic hydrocarbons; it is doubtful whether anyone would even consider such materials as possible food additives, but they might be contaminants from wrappings and machinery. The use of dogs in America is obligatory in the testing of food additives for general toxicity, so that their inclusion in carcinogenic tests makes no serious addition to conventional toxicity-testing programmes. However, the value of the dog for tests of either type is open to some doubt. Even though the ability of aromatic amines to produce bladder tumours in this species finally served to incriminate these materials as the cause of human bladder cancer, the sensitivity of the dog to other carcinogens is either small or unknown. Furthermore, the dog lives a long time, and it is generally believed that tests for carcinogenicity should entail the study of animals for the greater part of their life span. Finally, there is the question of numbers. Groups of dogs rarely exceed 6–8. The purpose of this type of screening procedure, as the Americans emphasize, "is largely one of experimentally detecting low levels of carcinogenic activity." This object seems unlikely to be achieved when small groups of a species are studied over less than half their natural life span. The common basis for both reports is the feeding of rats and mice with the largest tolerated doses of the test materials for their life span. The life span of rats and mice varies considerably in different laboratories, and there is clearly room for much improvement in standards of health maintained in the animal houses of experimental laboratories so as to reduce premature deaths from infection and other preventable conditions.

Since we remain ignorant of the nature of the process by which chemical substances produce cancer we shall have to remain content with this *ad hoc* type of testing until we understand more about the biochemical or other changes that precede the onset of malignant transformations. Meanwhile no one can suggest any short-term tests that would be appropriate for the detection of carcinogenic activity. It is perhaps a pity that the demonstration 20 years ago by B. D. Pullinger[3] that carcinogenic polycyclic hydrocarbons induced cellular changes in mouse skin within a day or two while non-carcinogenic substances did not has never been adequately exploited.

The final difficulty in interpreting the findings from such animal tests centres round the decision about

[1] Food Protection Committee, *Problems in the Evaluation of Carcinogenic Hazard from use of Food Additives*, 1959, Publication No. 749.
[2] *Monthly Bull. Minist. Hlth Lab. Serv.*, 1960, 19, 108.
[3] Pullinger, B. D., *J. Path. Bact.*, 1940, 50, 463.
[4] *Science*, 1960, 131, 697.
[5] See annotation, *Brit. med. J.*, 1960, 2, 1723.

what should be done with a compound shown to have carcinogenic properties under the conditions of these tests. The Ministry's report states simply that "no substance shown to be a carcinogen when administered *orally* to animals should be added to or allowed to contaminate food." A U.S. enactment states that no carcinogen is permitted in food. This problem of zero tolerances has been critically considered.[4] The U.S. experts discuss at some length with illustrations the fact that there is a dose-response curve for carcinogens of different types, and "safe doses" of some carcinogens have been demonstrated so far as this is possible. The report concludes with the advice that, while tolerance levels can be considered, "the vagueness of present knowledge" makes it undesirable to use any quantity of a carcinogen as a food additive unless banning "would constitute an important loss or hardship" or there is no reasonably good non-carcinogenic alternative.

In such an area of scientific uncertainty it still seems expedient to rely on the collective advice of a committee of experts such as is envisaged in the British recommendations rather than on the operation of the law as has been the tendency in the United States. The fact that two groups of experts, though sharing much common ground, differ significantly in their views on what are the best types of test is only to be expected when a scientific problem remains in the melting-pot. Perhaps more useful evidence will emerge from the operations of rival systems than from uniform obedience to a single set of recommendations. Clearly the time is not ripe for any attempt to settle such differences by international committees. More evidence from the laboratory is needed as a basis for new decisions, and no doubt the recently formed British Industrial Biological Research Association[5] will help to provide it.

FROZEN BLOOD

The increasing demand for large volumes of blood for such machines as the heart–lung oxygenator and kidney dialyser makes desirable the long-term storage of blood (especially blood belonging to the rare blood groups) which can be drawn upon to supplement the existing short-term storage banks. If blood is to be preserved over some years, the temperature of storage must be well below freezing point. The pioneer work of B. J. Luyet[1] showed that the haemolysis brought about by freezing could be minimized if blood is frozen below −120° C. and if freezing and thawing take place during a period of only a few milliseconds. But the practical problems of rapid heat exchange preclude this method for large volumes of blood. Considerable progress was made when A. U. Smith found that the addition of glycerol would protect red cells from damage, even when the rate of freezing was slow. It is probably the high concentration of salt in the unfrozen water which damages the red cells, and glycerol protects by holding water in the liquid state, thus reducing the rise in concentration of salt.[3] The disadvantage of glycerol lies in the fact that it must be removed before transfusion, because otherwise haemolysis occurs when the glycerol-laden red cells are mixed with normal plasma. Red cells stored with glycerol for 18 months can be deglycerolized either by dialysis in "cellophane" sacs[4] or by washing in decreasing concentrations of glycerol solution[5]; these cells survived well in the circulation after transfusion. Recent American work[6] has shown that the Cohn fractionator, a machine previously developed for separating blood into its component parts, can also be used for adding and removing glycerol. These workers have successfully transfused 1,014 units of blood which had been stored at −80° and −120° C. for periods up to 44 months. An average of 82% of the original cells taken from the donor reached the recipient, and the survival of these cells *in vivo* appeared to be good.

Another line of approach initiated by H. T. Meryman and E. Kafig[7] has been to add sugars to the blood before freezing. This allows the blood to be frozen over a period of a few seconds rather than a period measured in milliseconds and has the advantage that the sugars need not be removed before transfusion. Meryman and Kafig obtained good results by spraying blood containing 7% dextrose into liquid nitrogen (−195° C.). The recovered red cells were shown to survive well after transfusion. More recently R. G. Huntsman, B. A. L. Hurn, and H. Lehmann[8] have found that sucrose can also be used, with not more than 4–6% haemolysis on thawing. M. M. Strumia and his colleagues[9] obtained excellent results by using a mixture of dextrose and lactose as additives. A rapid rate of heat transfer was obtained by placing the blood in flat metal containers 3–4 mm. thick and freezing in an ethanol–CO_2 mixture at −79° C. The highest temperature at which these cells could be stored without deteriorating was −93° C. 80–90% of the cells were recovered intact, and these survived well after transfusion, even after storage for two years. Although Strumia handled only 20–50 ml. of blood at a time, it should be possible to use this relatively simple method for storing 500 ml., and work is already being carried out on this problem.[11]

[1] Luyet, B. J., and Gehenio, P. M., *Biodynamica*, 1940.
[3] Smith, A. U., *Lancet*, 1950, **2**, 910.
[3] Lovelock, J. E., *Biochim. biophys. Acta*, 1953, **11**, 28.
[4] Sloviter, H. A., *Lancet*, 1951, **1**, 823.
[5] Chaplin, H., Jr., Crawford, H., Cutbush, M., and Mollison, P. L., *ibid.*, 1954, **1**, 852.
[6] Haynes, L. L., *et al.*, *J. Amer. med. Ass.*, 1960, **173**, 1657.
[7] Meryman, H. T., and Kafig, E., *Proc. Soc. exp. Biol. (N.Y.)*, 1955, **90**, 587.
[8] Huntsman, R. G., Hurn, B. A. L., and Lehmann, H., *Brit. med. J.*, 1960, **2**, 118.
[9] Strumia, M. M., Colwell, L. S., and Strumia, P. V., *J. Lab. clin. Med.*, 1960, **56**, 576.
[10] —— —— —— *ibid.*, 1960, **58**, 587.
[11] Rinfret, A. P., *Ann. N.Y. Acad. Sci.*, 1960, **88**, 576.

NEW DRUGS IN THE TREATMENT OF RESPIRATORY INSUFFICIENCY

Alveolar hypoventilation leads to hypoxia and retention of carbon dioxide. Such a state of respiratory acidosis may be precipitated by any complication which severely impairs ventilation, or it may be persistent in patients

with chronic chest disease.[1] Mental disturbance usually occurs when the *p*H of arterial blood is less than 7.2 or the pCO_2 higher than 100 mm. Hg, and coma when the *p*H falls below 7.1 or the pCO_2 rises above 120 mm. Hg.[2] The logical treatment of respiratory acidosis is to employ measures to improve alveolar ventilation, but this is not always adequate. Acetazolamide has been given as an added form of therapy, but the results have been equivocal.[3] A. Naimark and colleagues have recently reported the use of dichlorphenamide in the treatment of 15 patients with chronic respiratory acidosis.[3] This drug has a capacity to inhibit carbonic anhydrase estimated to be thirty times that of acetazolamide. It was given in a dosage of 200 mg. daily for periods ranging from 2 to 30 weeks. All but one patient thought his symptoms improved, experiencing less dyspnoea, better effort tolerance, and a general sense of well-being. During administration of the drug there was a consistent rise in the arterial oxygen tensions and in the minute ventilation, in most cases with a slowing of respiratory rate and an increase in tidal volume. Hypercapnia was much decreased in all patients but one. The authors suggest that, in addition to a renal effect, dichlorphenamide has an effect on the respiratory centre, resulting in an increase in ventilation and lowering of pCO_2.

G. G. Nahas[4] has shown that the organic carbon dioxide buffer, trihydroxymethylaminomethane (known as TRIS or THAM), can prevent acidosis and hypercapnia in dogs rendered artificially apnoeic. G. L. Brinkman and colleagues[5] have recently studied the effect of intravenous doses of 20 g. of THAM in four patients with chronic respiratory acidosis. They found that in all cases it raised the arterial *p*H but lowered the minute ventilation and the arterial pO_2. Except in one case in which it was reduced, the arterial pCO_2 remained at approximately the same level throughout the study, in spite of the reduction in respiratory minute volume. These workers attributed this to the increase in urinary excretion of bicarbonate. THAM was also effective in raising the arterial *p*H in two other cases with severe respiratory acidosis. One patient regained consciousness two hours after its administration and the arterial pCO_2 fell from 160 to 68 mm. Hg. The drug, which was given by infusion through a gastric tube in both cases, caused diarrhoea during the infusion and produced tetany as the acidosis was relieved. Hypoglycaemia did not occur, though this has been reported elsewhere as following intravenous infusion.[6]

F. Manfredi and colleagues[7] have also given intravenous THAM in three cases of severe respiratory acidosis. All were in extremis, and one died within twenty minutes of starting the infusion. The two other patients, both with tracheotomies and under respirator treatment, improved after the arterial *p*H rose and the pCO_2 fell, although the total serum carbon dioxide increased. These authors suggest that during infusion of THAM large amounts of carbon dioxide are drawn from the saturated tissues into the blood, and that the excretion of bicarbonate in the urine and the amount of carbon dioxide in the expired air are both increased.

The clinical information on dichlorphenamide and THAM is at the moment very limited. Their modes of action are not yet fully understood. If further information is as encouraging as these preliminary reports, there will surely be a place for these drugs as adjuncts to the treatment of respiratory insufficiency.

[1] Baldwin, E. de F., Cournand, A., and Richards, D. W., *Medicine (Baltimore)*, 1949, **28**, 201.
[2] Wentlake, E. K., Simpson, T., and Kaye, M., *Quart. J. Med.*, 1955, **24**, 155.
[3] Naimark, A., Brodovsky, D. M., and Cherniack, R. M., *Amer. J. Med.*, 1960, **28**, 368.
[4] Nahas, G. G., *Science*, 1959, **129**, 782.
[5] Brinkman, G. L., Remp, D. G., Coates, E. O., and Priest, E. Mc., *Amer. J. med. Sci.*, 1960, **239**, 341.
[6] Tarail, R., and Bennett, T. E., *Proc. Soc. exp. Biol. (N.Y.)*, 1959, **102**, 208.
[7] Manfredi, F., Sieker, H. O., Spoto, A. P., and Saltzman, H. A., *J. Amer. med. Ass.*, 1960, **173**, 999.

RADIATION HAZARDS

A more explicit knowledge of the hazards to man of nuclear radiations has been gained since the Medical Research Council's report by its special committee on this subject appeared in 1956.[1 2] The second report of the committee,[3] out last week, gives due weight to the latest information, but still emphasizes the need "for further intensive research." Despite admitted gaps, it interprets the known data as best it may. Some of the main conclusions are referred to here, but it is hoped to discuss the report more fully in these columns at a later date.

On the controversial question of "permissible doses of radiation," the committee finds it "impossible to state categorically that any dose of radiation will be entirely without consequence." But levels must be set for practical use. The report therefore recommends "maximum permissible levels" for individuals, for various groups, and for the general population. The idea of a "threshold dose" below which no harm will result does not find favour, because it oversimplifies a complex situation in which doses of radiation must be measured against both the changes they cause in the body and the contrary changes wrought by the body's reparative powers. The assessment of damage caused by low doses of radiation is itself noted to be a troublesome problem leading only to tentative results.

Much the largest single source of radiation for the general population is the natural background, with a dose-rate of about 100 millirads a year. Next to that is medical radiology, about 20 mr, and then nuclear fall-out at 1.2 mr (up to November, 1958, averaged over 30 years). Whether radiation plays any part in causing the increased incidence of some forms of leukaemia in recent years is impossible to assess, says the report; present evidence "suggests that other factors must be implicated and that the effect of radiation is likely to be relatively small." Discussing the question of *x*-raying the pregnant woman's abdomen the report concludes, like the recently published second report of the Adrian Committee,[4] that it is prudent to keep such

[1] *The Hazards to Man of Nuclear and Allied Radiations*, Medical Research Council, 1956, London. H.M.S.O.
[2] *Brit. med. J.*, 1956, **1**, 1418.
[3] *The Hazards to Man of Nuclear and Allied Radiations*, Second Report, Medical Research Council, 1960, London. H.M.S.O. See summary at p. 1967 of this journal.
[4] See *Brit. med. J.*, 1960, **2**, 1720, 1727.

radiography at the lowest practicable level, for the existence of a risk, though not substantiated, has not been disproved either. The Adrian Committee emphasized, too, as does the present report, that improvements in equipment and technique could greatly help to reduce the dosage from medical radiography in general.

FEMALE HIRSUTISM

Hirsutism in women means that the hair has a masculine quality and distribution. The term is somewhat relative, and such factors as the patient's age and race should be considered before using it in a pathological sense. An overgrowth of facial hair is common after the menopause, and moderate hirsutism may be regarded as normal in many young women of Mediterranean stock.

Hirsute women occasionally have a major endocrine disorder, such as adrenocortical tumour or hyperplasia, or virilizing tumour of the ovary. The hirsutism then tends to be rapidly progressive and accompanied by amenorrhoea and signs of virilization. In a somewhat larger group it is a manifestation of the Stein–Leventhal syndrome of bilateral fibrocystic ovaries. Other symptoms are amenorrhoea or oligomenorrhoea, infertility, and often obesity; the 17-ketosteroids are normal or moderately raised. Hirsutism may also result from androgen therapy, often unavoidably in treating cancer of the breast, but inexcusably in the management of menstrual disorders.

Most cases fall into the group of so-called idiopathic or simple hirsutism, and until recently there was little evidence on the nature of the endocrine disorder. Hypersensitivity of the hair follicles to endogenous androgen was put forward as a possible explanation. As in the Stein–Leventhal syndrome, the 17-ketosteroids are normal in amount or moderately raised (above 16 mg. but seldom above 25 mg. a day). When raised, they can be readily suppressed by cortisone or its analogues, which points to their adrenal origin. Acne vulgaris and minor menstrual disorders are common in this group.

New methods of investigation are disclosing minor errors of steroid metabolism in an increasing proportion of cases. For example, the excretion of androsterone and aetiocholanolone, both weak androgens, may exceed normal,[1 2 12] and less commonly the urinary dehydroisoandrosterone,[3 4] another weak androgen, and rarely pregnanetriol,[5] are increased. More recently A. M. Moses and colleagues[6] have reported that infusions of A.C.T.H. cause a disproportionate rise in the excretion of 17-ketosteroids over 17-hydroxycorticoids in hirsute women when compared with normal controls. This has been confirmed by J. W. Goldzieher and H. Laitin.[7] The evidence, though very indirect, thus points to a bias by the adrenal glands towards the secretion of androgens, at least in some cases of simple hirsutism. Against such a background it is possible, as I. E. Bush and V. B. Mahesh have pointed out,[2] that emotional or other factors may trigger off hirsutism by causing repeated release of corticotrophin.

The treatment of female hirsutism is unsatisfactory. In the Stein–Leventhal syndrome, wedge resection of the ovaries usually corrects infertility and restores normal menstrual rhythm, but does not alleviate the hirsutism or suppress any associated excess in the excretion of 17-ketosteroids or their fractions. In both the Stein–Leventhal syndrome and in simple hirsutism, treatment with moderate doses of cortisone or its analogues will correct the abnormalities in excretion of 17-ketosteroids. W. H. Perloff and his colleagues claim that this also benefits the hirsutism.[8 9] Other workers had less success with steroids,[10 11] and it is possible that the treatment may have to be continued, perhaps for several years, to achieve a maximal effect. It is arguable whether the risks of prolonged steroid therapy are justifiable in a condition which carries no morbidity. These risks, however, must be carefully weighed in each patient against the psychological trauma of hirsutism, which may be serious in young women, and the degree of the errors in steroid metabolism.

Local treatment of hirsutism includes the removal of excessive facial hair, temporarily by wax or permanently by electrolysis. The last procedure may be painful and is very time-consuming and beyond the means and endurance of most women. It is available in a few centres under the N.H.S., but the waiting-lists are long. In the end most patients will resort to shaving and the aid of special make-up. It is probably a mistake to think that this aggravates the hirsutism.

[1] Kappas, A., Pearson, O. H., West, C. D., and Gallagher, T. F., *J. clin. Endocr.*, 1956, **16**, 317.
[2] Bush, I. E., and Mahesh, V. B., *J. Endocr.*, 1959, **18**, 1.
[3] Jailer, J. W., and Vande Weile, R. L., *Gynaecologia (Basel)*, 1954, **138**, 276.
[4] Gardner, L. I., *J. clin. Endocr.*, 1953, **13**, 1054.
[5] Zacco, M., Dalfino, G., Piliego, N., and Leonardi, M., *Folia endocr. (Pisa)*, 1957, **10**, 619.
[6] Moses, A. M., Klaiber, E. L., Lobotsky, J., Jacobs, R. D., and Lloyd, C. W., 42nd Meeting of the American Endocrinology Society, June 9–11. 1960.
[7] Goldzieher, J. W., and Laitin, H., *J. clin. Endocr.*, 1960, **20**, 967.
[8] Perloff, W. H., Hadd, H. E., Channick, B. J., and Nodine, J. H., *A.M.A. Arch. intern. Med.*, 1957, **100**, 981.
[9] —— Channick, B. J., Suplick, B., and Carrington, E. R., *J. Amer. med. Ass.*, 1958, **167**, 2041.
[10] Mattingly, D., Mills, I. H., and Prunty, F. T. G., *Brit. med. J.*, 1960, **1**, 1298.
[11] de Mowbray, R. R., Spence, A. W., Medvei, V. C., and Robinson, A. M., ibid., 1959, **2**, 456.
[12] Behrman, H. T., *J. Amer. med. Ass.*, 1960, **172**, 1924.
[13] Lidsett, M.B., and Riter, B., *J. clin. Endocr.*, 1960, **20**, 180

PROSTATIC ABSCESS IN EARLY INFANCY

Abscess of the prostate gland occurs rarely during the first year of life. A few cases have been reported during childhood, but only five which have occurred within the first year,[1–5] and all after normal birth. A possible cause suggested[1] is a transient bacteriaemia occurring in association with the hypertrophy and secretory activity of the prostate during the first month of life, a similar condition being the hypertrophy and secretion of the mammary gland which sometimes also is associated with abscess formation at the same stage of

[1] Alison, F., and Le Tan Vinh, *Nourrisson*, 1952, **40**, 15.
[2] Boy, J.-L., Wallon, D., and Lauras, H., *Arch. franç. Pediat.*, 1953, **10**, 1071.
[3] George, P. A., *Gt Ormond Str. J.*, 1953, No. 5, 58.
[4] Innes Williams, D., and Martins, A. G., *Arch. Dis. Childh.*, 1960, **35**, 177.
[5] Giannattasio, R. C., *N.Y. St. J. Med.*, 1960, **60**, 3471.

development. It has further been suggested[3 4] that the abscess is a secondary metastatic one from a primary umbilical sepsis, or secondary to a periprostatic haematoma of unknown origin. Necropsy on the one fatal case[1] showed a large prostatic abscess cavity and dilated ureters and pelves of the kidney. Small disseminated abscesses of the renal parenchyma were present. There was no local congenital malformation in this case, and none was noted in any of the surviving cases.

The infants all had pyrexia and leucocytosis. Retention of urine, with a subumbilical abdominal mass, was present in four cases, and in all a midline swelling which resembled a prostatic tumour was readily palpable per rectum. Two patients had a raised blood urea which fell rapidly to normal after appropriate treatment; two had an infection of the urine, the organism cultured being the same as that obtained from the pus in the prostatic abscess. An associated epididymitis was present in one case.

Four patients were treated by preliminary catheterization and then aspiration of the abscess per rectum or by the perineal route, together with antibiotics, the fifth with antibiotics only. Spontaneous rupture should be averted because of the risk of the formation of a recto-urethral fistula. It is not necessary to leave an indwelling catheter in position, as micturition occurs spontaneously after drainage of the abscess. Resolution of the condition is usually rapid provided the abscess is adequately drained. D. I. Williams and A. G. Martins recommend that the cavity be kept empty by daily "stripping" digitally of the area per rectum. In all these cases the responsible organism was a staphylococcus, which was sometimes accompanied by an enterococcus.

NOISES OFF

A survey carried out at the Royal Northern Hospital in London showed that about half of the patients questioned on the subject had complaints to make about noise.[1] The voices of fellow patients or staff, particularly at night or in the early morning, caused the most trouble. A further investigation[2] by the King Edward's Hospital Fund for London confirms the original finding reported two years ago[3] that only about half the patients in hospital admit to being bothered by noise, but the King's Fund investigators found that the biggest single cause of complaint was not the human voice in the hospital but traffic outside it. To exclude the noise of traffic from many hospital wards is impracticable, but when new hospitals are being planned wards should be sited in such a way that this source of serious discomfort to patients is avoided.

The recent report of the King's Fund mentions that, of the disturbing noises made by other patients, the most distressing were those made by the very ill or those recovering from anaesthetics. This is overcome in some hospitals by putting noisy patients into soundproof cubicles or in side-wards; a noise-reducing hood has been devised to fit over the head of hospital beds.[4] Noisy equipment is still a cause of complaint in many hospitals, and the report emphasizes the importance of the proper maintenance of equipment so that trolleys do not rattle and squeak, doors do not bang, and taps do not drip. Radio is mostly piped to earphones, or should be, but television can cause great annoyance, especially when all the patient can see is the back of the set.[5] Nevertheless the King's Fund report honestly records the remark of one patient (no doubt a juke-box addict): "I don't think there is enough noise. Music would be suitable." One hospital spokesman summed up the lessons learned in trying to reduce noise by saying: "Our experience is that the greatest single factor in controlling noise is staff discipline."

[1] Statham, Cecily, *Brit. med. J.*, 1959, **2**, 1247.
[2] *Noise Control in Hospitals*, 1960. Obtainable from King Edward's Hospital Fund for London, 34 King Street, London E.C.2. Price 1s., post free.
[3] *Noise Control in Hospitals*, 1958. See annotation *Brit. med. J.*, 1958, **2**, 1282.
[4] Catchpole, B. N., *Brit. med. J.*, 1960, **2**, 462.
[5] Marshall, Struan G., ibid., 1960, **1**, 61.

CHRONIC BRONCHITIS AS A PATHOLOGICAL ENTITY

The cardinal symptom of chronic bronchitis is the habitual expectoration of mucoid sputum. Any other symptoms such as febrile attacks, haemoptysis, and sustained or recurrent dyspnoea may coexist, but are not essential for the clinical diagnosis. The mucus derives from mucous glands and goblet cells in the bronchi, so that pathological diagnosis must depend on specific changes in these structures.

Lynne Reid[1] has recently studied this matter, concentrating on the glands, which are volumetrically much the more significant, rather than the goblet cells, which are uneven in distribution and are often damaged in necropsy material. Measuring the thickness of the bronchial wall from the basement membrane to the inner aspect of cartilage, and the thickness of the gland at the same point, she found that the increased thickness of the wall in chronic bronchitis was almost wholly attributable to gland thickening. The gland–wall ratio increased from 0.26 to 0.59 from normals to bronchitics. In addition, the mucous cells were greatly increased in number and distended with secretion. These changes existed only in patients with a habitual mucoid sputum, and were absent in three patients with emphysema who had had no more than an occasional trace of sputum. Further, the degree of change in the glands varied with the volume of sputum, being greatest in patients who had previously expectorated more than an ounce each day.

The clinical significance of these observations is not immediately obvious, and more needs to be known of the behaviour of the glands in asthma, although J. C. Houston and colleagues[2] suggest that no such changes occur in that disease. However, on the existing evidence, it seems that a habitual mucoid sputum, or chronic bronchitis, derives principally from overactivity of mucous glands, which can be demonstrated pathologically, and that associated changes attributable to asthma and emphysema need not necessarily coexist.

[1] Reid, L., *Thorax*, 1960, **15**, 132.
[2] Houston, J. C., De Navasquez, S., and Trounce, J. R., ibid., 1953, **8**, 207.

HAZARDS TO MAN OF NUCLEAR AND ALLIED RADIATIONS

The Second Report of the Medical Research Council's Committee on Hazards to Man of Nuclear and Allied Radiations† was published on December 21. Below we print, unabridged, a digest of the Report prepared by the M.R.C. Headquarters Staff, together with a list of the subjects and authors of the Report's eleven technical appendices.*

DIGEST OF REPORT

This Report, of the Committee originally appointed by the Medical Research Council in 1955 in response to a request from the Prime Minister, takes into account increases in knowledge of the effects of ionizing radiations which have accumulated since their first Report in 1956 (*The Hazards to Man of Nuclear and Allied Radiations.* Cmd. 9780). It follows the general pattern of the earlier publication. The main chapters review the general field of radiation and its biological effects, the levels of radiation that exist at present and those that may be expected to occur in the future; and the possible hazards of exposure to radiation are also assessed The technical background is given in eleven appendices. The Report indicates that, although a great deal of new information is available, there are still many gaps in knowledge of the effects of radiation, and that further intensive research is accordingly still necessary.

The Report again emphasizes the difficulty of assessing the significance of radiations in absolute terms. Instead it makes use of the dose of radiation received from natural background as a reference level. In the United Kingdom this dose is, on average, about 100 millirads per year. By comparison, the doses received both from the increased use of radiation in modern life and from radioactive fall-out are extremely small.

RADIATION AND ITS EFFECT ON THE HEALTH OF THE INDIVIDUAL

Leukaemia

The mortality from this disease has been rising for over 20 years in all countries for which data are available; in England and Wales the death rate from various forms of leukaemia was 17 per million persons in 1931, 42 in 1950, and 56 in 1959. Most of the recorded increase has occurred in the older age groups, and in great part may be accounted for by increased recognition of the disease as a result of improvements in the medical care of the elderly. However, there does seem to have been a real increase in the incidence, among younger people, of two forms of the disease, acute leukaemia and chronic myeloid leukaemia, and it is known that these two forms of leukaemia can be produced by high doses of radiation received in special circumstances. Nevertheless, until there is more evidence on the effects of lower doses, it will be impossible to assess directly whether any part of the increased incidence now being observed in the general population is due to increased exposure to radiation. All the evidence that is at present available suggests that other factors must be implicated and that the effect of radiation is likely to be relatively small.

Special studies have been undertaken to investigate the possible causes of the variation in the incidence of leukaemia in different regions of this country. These investigations have shown that no single factor will account for the differences, and have led the Committee to believe that local differences in radiological practice or in the natural background radiation cannot play more than a very small part. In two of the cities in the United Kingdom which were studied in great detail the difference in radiation exposure was estimated to have accounted at most for about 1% of the observed difference in leukaemia mortality.

The most complete information on the relation between exposure to relatively high doses of radiation and the incidence of leukaemia in man is provided by two continuing investigations: the study of the incidence of leukaemia in Hiroshima and Nagasaki and the surveys which are being sponsored by the Medical Research Council on the incidence of leukaemia in patients treated by radiation for ankylosing spondylitis, a disease of the spinal column. In the populations exposed at Hiroshima and Nagasaki to heavy irradiation from the atomic bombs in 1945 there has been a significant excess of cases of leukaemia. It has also been demonstrated that the incidence of leukaemia decreased with increasing distance from the bombs—that is, with diminishing doses of radiation. Results from this study that have become available since 1956 have shown a peak incidence of leukaemia in 1951, 1952, and 1953—that is, during the sixth, seventh, and eighth years after exposure to radiation. Since that time the incidence has diminished, although in 1957 it was still higher than the expected frequency in a comparable non-irradiated Japanese population. This information is not inconsistent with the results from the survey of patients irradiated for ankylosing spondylitis, which has indicated that the increased risk of inducing leukaemia in these different circumstances is diminishing by the tenth to twelfth years after exposure. As a result of the important evidence from these studies, the Committee now feel that they can assert with some confidence that the increased risk of leukaemia following high doses of radiation would be likely to decline after the lapse of a decade, and that an individual once exposed is not at uniformly increased risk for the whole of the rest of his life.

The Committee have also reviewed the evidence on the possibility that radiographic examination of the pregnant woman's abdomen or pelvis may add to the small natural chance that her child might develop leukaemia during the early years of its life. The results of the earlier studies of the leukaemogenic effect of irradiation *in utero* have not been substantiated by subsequent extensive investigations. However, the possibility that a small risk exists has not been disproved, and it would therefore seem prudent to reduce radiographic examination of the abdomen and pelvis of the pregnant woman to the lowest practicable level.

Cancer

Recent evidence made available by the Tumour Registry in Hiroshima indicates that there is an excess in the death-rate from cancer among the Japanese survivors of the atomic bomb explosions, and that it is highest amongst those who were closest to the exploding bombs. It is too early to say whether this increase in mortality affects all forms of cancer and whether it has reached its highest point, but other evidence suggests that the average latent period for the indication of cancer following irradiation is more than 10 years.

Effects of Variations in Dose-rate

The biological effects of a given amount of radiation are related both to the intensity of radiation, as measured by the dose given in a unit of time, and also to the length of time over which the exposure is spread. Knowledge of the frequency and types of radiation injury in man comes from situations in which relatively large doses of radiation have

*_The Hazards to Man of Nuclear and Allied Radiations: A Second Report to the Medical Research Council_, 1960, Cmnd. 1225. H.M.S.O., London. Price 7s. net.

†Sir Harold Himsworth, F.R.S. (*Chairman*); Dr. E. E. Pochin (*Vice-chairman*); Sir John Cockcroft, O.M., F.R.S.; Professor A. Haddow, F.R.S.; Professor A. Bradford Hill, F.R.S.; Dr. J. F. Loutit; Dr. W. G. Marley; Professor K. Mather, F.R.S.; Professor W. V. Mayneord; Professor P. B. Medawar, F.R.S.; Professor J. S. Mitchell, F.R.S.; Professor L. S. Penrose, F.R.S.; Dr. F. G. Spear; Professor J. R. Squire; Dr. A. C. Stevenson; Professor C. H. Waddington, F.R.S.; Professor B. W. Windever; Mr. E. D. T. Jourdain (*Assessor from the Agricultural Research Council*). Others serving during the period covered: The late Sir Ernest Rock Carling and Sir Edward Salisbury, F.R.S. Secretariat: Dr. W. M. Court Brown; Dr. B. S. Lush; Dr. R. C. Norton.

been received at high rates—as, for example, during radiotherapy or at the moment of the nuclear explosions over Hiroshima and Nagasaki. Recently, in a number of investigations of the somatic effects of radiation on mice, moderate as well as high dose-rates have been used. In these experiments it was found that the response to a dose of radiation given over a long period of time—that is, at a low dose-rate—was less than that to the same dose given at a high rate. If these experimental findings are extended and can be taken to be applicable to man, previous estimates of the effects of radiation at low dose-rates based on the assumption that such effects are directly proportional to the total accumulated dose, irrespective of the rate at which it is received, may prove to have been too high. The Committee feel that further study of this problem is of great importance because the radiation to which man is exposed from the natural background and from fall-out is received at very low dose-rates.

"Threshold" Dose of Radiation

The Committee stress that any general concept of a single "threshold" or minimum dose of radiation below which no effect will be produced is an oversimplification and therefore misleading. Although there is sufficient knowledge to allow an approximate assessment of the damage which might be expected from high and moderate rates of exposure to radiation, the likely effects of low rates of exposure can only be inferred in a rather tentative way. Accordingly, the Committee consider that it is prudent to continue to assume that even the lowest doses of radiation may involve correspondingly small, though definite, probability of adverse effect. They feel that, although this attitude may be unduly cautious, it is the only justifiable one in the present state of knowledge.

GENETIC EFFECTS OF RADIATION

The Committee draw attention to the increase in knowledge about human chromosomes and the demonstration, predicted in their 1956 Report, that some hereditary diseases are associated with chromosome abnormalities. However, there is little evidence to indicate whether or not this type of abnormality can be produced by radiation, and it is considered wise, at present, to adopt a cautious approach to this problem.

In 1956 it was considered that the number of new mutations induced in any individual by radiation was directly proportional to the total dose of radiation that he or she had received. A certain amount of evidence has since been obtained from animal experiments suggesting that, at least as far as the particular mutations studied are concerned, the effect may be substantially reduced if the total dose is received at a low rather than a high dose-rate. As mentioned above, radiation from natural background and fall-out is received at very low dose-rates, and it would therefore be reasonable to infer, if further evidence confirms these findings, that any mutations induced by radiation from these sources might prove to be fewer than have hitherto been estimated.

EXISTING AND FORESEEABLE LEVELS OF EXPOSURE TO RADIATION

Medical Radiology

In the 1956 Report it was recommended that a review of radiological practice should be undertaken to establish the true position in this country, and a committee appointed by the Secretary of State for Scotland and the Minister of Health, under the chairmanship of Lord Adrian, have concluded a nation-wide survey of the hazards to patients from all medical radiological procedures. In their second Report,‡ published on December 7, they have calculated that the annual total contribution to the genetically effective dose to the population from all forms of medical radiology was 19.3 mr. This is less than the previous estimate for diagnostic radiology alone, given in the Medical Research Council's 1956 Report. However, medical radiology contributes a bigger dose than any other source of man-made radiation, and the Adrian Committee consider that the dose could be reduced to 6 mr., without curtailment of essential radiological services, if greater consideration were given to improvements in technique.

‡See *Brit. med. J.*, December 10, pp. 1720 and 1727.

Occupational Exposure to Radiation

The Committee have considered the recommendations of the International Commission on Radiological Protection concerning permissible levels of occupational exposure to ionizing radiation, and (as mentioned below in the section on the Assessment of Hazards of Exposure to Radiation) they conclude that, in general, these form a satisfactory basis for radiation protection at the present time. They have also reviewed the doses received by workers in the United Kingdom who are exposed to radiation in industrial, medical, and other occupations. They estimate that in spite of the increase in the use of ionizing radiations the genetically effective dose as averaged over the whole population from the exposure of such workers is at the present time only about 0.5% of that from natural background radiation.

Fall-out from Nuclear Weapon Explosions

In 1956 little information was available on the amount and distribution of radioactive fall-out from nuclear weapon explosions. However, in recent years there have been extensive observations of radioactivity at various levels in the atmosphere, in water, food, herbage, and other materials. In particular, the Agricultural Research Council maintain a most comprehensive monitoring programme of the amounts of radioactive materials from fall-out in human diet in the United Kingdom, and this work, together with that of the Atomic Energy Authority, has provided much information on the mechanisms involved in the passage of materials from fall-out into the human body.

From direct measurements it is now known that the "reservoir" of fission product radioactivity in the upper atmosphere or stratosphere is smaller than was estimated earlier—for example, by the United Nations Scientific Committee on the Effects of Atomic Radiation in 1958. It is also known that the rate and nature of the fall-out is influenced by the site and pattern of weapon testing. The radioactive debris released into the stratosphere by explosions in tropical latitudes may take a considerable time, months or perhaps years, before it is transferred to the lower atmosphere and deposited on the ground. Consequently a large proportion of the original radioactive atoms decay before reaching the earth. On the other hand, radioactive debris injected into the stratosphere in high latitudes, particularly in the autumn, is deposited fairly rapidly; the deposit containing a higher proportion of nucleides which have a short half-life. Although many of the fission product nucleides are taken up into the body sparingly, and thus contribute little to the "internal" radiation dose from fall-out, many of them emit penetrating gamma rays as they decay and temporarily give rise to an increase in the "external" gamma radiation to which the body is exposed.

Strontium-90

The Report contains a detailed account of the ways in which the long-lived fission product strontium-90 may be transferred from fall-out through the food chain into human bone. An important finding since 1956 is that the uptake of the isotope by the roots of plants, the magnitude of which is related to the total accumulated fall-out remaining in the soil, is at present of minor significance compared with the direct uptake by the parts of the plant which are above ground. It has also been established that at present the proportion of strontium-90 absorbed by plants in the latter way is dependent on the rate of fall-out, rather than on the accumulated total. Consequently the amount of strontium-90 eventually taken into the body and deposited in bone will be related to the current rate of fall-out, and as environmental contamination with radioactive material diminishes the levels of strontium-90 in bone should gradually decrease.

From the extensive monitoring of foodstuffs carried out by the Agricultural Research Council it is possible to make estimates of the average concentration of strontium-90 in the national diet. Measurements of the levels of strontium-90 in samples of human bone made jointly by the Medical Research Council and the Atomic Energy Authority have been greatly extended since 1956, and correlation of the results from both dietary and bone surveys have shown that values for strontium-90 to be expected in bone can be derived from the measured levels in the diet.

The average levels of strontium-90 which have been observed both in the diet and in human bone in the United Kingdom are such as to make it extremely unlikely that there has been any appreciable hazard to human health from this isotope.

Caesium-137

Much new information about caesium-137 has also become available since 1956. This isotope has a long half-life of about 30 years, but remains in the body for an average time of only about 4 months, a minority of its atoms decaying during this time and leading to the emission of gamma rays. The estimated gonad dose-rates from caesium-137 are about 1 mrad per year in 1958 and 1–1.5 mrads per year in 1959. As the extent to which caesium-137 is taken up by plants and transferred through the food chain into the body is also determined largely by the current rate of fall-out, the dose-rate to the gonads from "internal" caesium-137 will gradually fall as environmental contamination decreases, although "external" irradiation from the accumulated deposit on the ground will continue for some time.

Carbon-14

Most of the carbon-14 produced by nuclear explosions is still in the atmosphere, but it will slowly become more widely dispersed. It has been estimated that the dose of radiation to the gonads from this carbon-14 will be 10 mrems during the generation of 30 years commencing in 1954, and will fall to 5 mrems during the next 30-year period, the doses in subsequent generations becoming much lower. (These values are to be compared with 3,000 mrem received from natural sources during each 30-year period.)

The total dose, delivered during some hundreds of generations, will be about 120 mrem, which is approximately equal to that received from natural sources during any one year. Some additional genetic effects may result from the "transmutation" of the carbon-14 to nitrogen-14 during its radioactive decay, but these are likely to be fewer in number than those induced by the radiation emitted at the time of the decay.

Summary of Present and Foreseeable Doses to the Gonads

In estimating the genetic effect of radiation from different sources, the dose accumulated over the 30-year period of a generation is thought to be the relevant dose to be taken into consideration. The average annual dose-rates corresponding to these 30-year integrated doses from various sources are summarized below.

Gonad Dose Levels

Source of Radiation	Average Annual Dose-rate (Millirads per Year)
Natural background	Range: 85–106
Medical radiology: 1957 level	19
Miscellaneous sources	Less than 1
Occupational exposure: 1959 level	0·5
Fall-out:	
Maximum value for mean dose-rate in any 30-year period from nuclear explosions up to November, 1958	1·2
(Average value over five-year period 1955–9: 2·4 mrads year)	
(Dose-rate in July, 1959: 6 mrads/year)	

Possible Doses from Fall-out under Conditions of Continued Weapon Testing

The Committee emphasize that any attempt to forecast the dose-rates that might have followed the continuation of weapon testing involves a large amount of conjecture since the levels would depend on many factors, including the amount of testing and the pattern and nature of the explosions. They have, however, attempted to estimate the dose-rates that would have resulted in this country if nuclear explosions had been continued indefinitely after 1958 so as to produce the same rate of fall-out as the average for the period January, 1958, to July, 1959. The Committee have estimated that, under such conditions, when equilibrium was reached in about 100 years' time the average gonad dose-rate might be raised to about one-seventh, the dose-rate in new bone to about one-half, and that in bone-marrow up to about one-fifth of that received from the natural background radiation. They cannot, however, exclude the possibility that, even for the rate of fall-out assumed, the doses might be several times higher or lower.

ASSESSMENT OF HAZARDS OF EXPOSURE TO RADIATION

Permissible Doses of Radiation

The Committee feel that it is impossible to state categorically that any dose of radiation will be entirely without consequence, and that it is advisable to set levels of radiation which should not be exceeded. These levels must be based on practical considerations which balance the possible risks of harm against the advantages of using radiation in particular circumstances. They have accordingly recommended "maximum permissible levels" of radiation for individuals, for the general population, and for various groups within the population.

The highest maximum permissible levels are for the "occupationally exposed" group, but the Committee stress that just as endeavours are made in any other industry to lower all risks to workers as much as possible, every effort should be made to reduce exposure to the lowest practicable level below that considered permissible.

For any fractions of the general population which are not exposed to radiation in the course of their work, but may be brought into closer contact with it than the population in general, the maximum permissible level of exposure is set lower than that for radiation workers, since such populations may include children, whose tissues are more sensitive to some effects of radiation than are those of adults. Moreover, the special medical supervision and personal monitoring procedures applied to those who are occupationally exposed do not apply to members of the general public.

The average maximum permissible level for the population of the country as a whole is set even lower, since a dose which could be incurred by a small fraction of the population, without harm to its members or appreciable genetic risk to their families, might nevertheless have significant genetic effects if incurred by the population as a whole.

In advising upon the maximum permissible doses which may be received by these groups, the Committee have, subject to certain qualifications, endorsed the recommendations of the International Commission on Radiological Protection which were adopted by the Commission in September, 1958, and extended in 1959.

Permissible Levels of Strontium-90

In their 1956 Report the Committee said that "the maximum allowable concentrations of radiostrontium in the bones of the general population, with its proportion of young children, should not be greater than 100 micromicrocuries of strontium-90 per gramme of calcium." Subsequently the International Commission on Radiological Protection recommended that for contamination with material such as strontium-90, the radiation from which is confined mainly to one type of tissue, the permissible average level for the general population should not exceed one-thirtieth of that regarded as permissible for individuals who are occupationally exposed to radiation; and that in no individual in the ordinary population should one-tenth

of the occupational level be exceeded. The occupational level now recommended by the Commission is equivalent to 2,000 micro-microcuries of strontium-90 per gramme of calcium. On this basis the maximum permissible concentration of strontium-90 in bone averaged over the whole population would be 67 micro-microcuries per gramme of calcium; and the maximum for any individual member of the population would be 200 micro-microcuries per gramme of calcium.

The Committee point out that these recommendations refer to the permissible levels when strontium-90 is the sole source of radiation in bone additional to that received from the natural background and medical radiology, and they accept them in this sense.

In 1956 there was great uncertainty about all aspects of the problem presented by strontium-90. In particular, the Committee had little information on the extent to which the concentrations in bone might continue to rise even if nuclear weapon-testing should cease. They therefore made the precautionary recommendation that immediate consideration would be required if the concentration of strontium-90 in human bone showed signs of rising greatly beyond 10 micro-microcuries per gramme of calcium.

With increased knowledge of the factors which determine the levels of strontium-90 in newly formed bone the Committee do not now envisage, as they did in 1956, that bone concentrations of this isotope would continue to rise considerably after a decrease or cessation of weapon testing. Nevertheless, since they cannot at present reckon all additional sources which contribute to the irradiation of bone or bone-marrow, they still think it wise to adopt a cautious attitude. They recommend, therefore, that if the concentration of strontium-90 in bone, calculated as an average for any age-group, including the groups of infants and young children, was found to be rising continuously and to have reached the level of one-half of that recommended as the maximum permissible level for the population as a whole, a reassessment of the situation would be required. The present cautionary level therefore corresponds to an average value of 33 micro-microcuries of strontium-90 per gramme of calcium in human bone at any age.

TECHNICAL APPENDICES

The Report concludes with eleven appendices, which together comprise over two-thirds of its total length. Their subjects and authors are as follows:

Appendix A.—"Changes in the National Mortality from Leukaemia," by W. M. Court Brown and R. Doll.

Appendix B.—"The Leukaemogenic Effect of Whole-body Irradiation of the Mouse: Experimental Work at the Radiobiological Research Unit, Harwell," by R. H. Mole.

Appendix C.—"Recent Information on the Genetical Effects of Radiation: A Bibliography and Notes," by L. S. Penrose and A. C. Stevenson.

Appendix D.—"Gamma-ray Dose-rates to Human Tissues from Natural External Sources in Great Britain," by F. W. Spiers.

Appendix E.—"Naturally-occurring Alpha Activity," by W. V. Mayneord.

Appendix F.—"Changes in the Levels of Radioactive Fall-out and the Resulting Radiation Doses to Man in the United Kingdom," by J. F. Loutit, W. G. Marley, W. V. Mayneord, and R. S. Russell. *Annexe:* "Possible Levels of Fall-out Under Conditions of Continued Weapon Testing," by G. W. Dolphin, J. F. Loutit, W. G. Marley, W. V. Mayneord, and R. S. Russell.

Appendix G.—"Occupational Exposure to Radiation in the United Kingdom and its Contribution to the Genetically Effective Dose," by W. Binks and W. G. Marley.

Appendix H.—"The Nuclear Reactor Accident at Windscale—October, 1957: Environmental Aspects," by J. F. Loutit, W. G. Marley, and R. S. Russell.

Appendix J.—"Maximum Permissible Dietary Contamination after the Accidental Release of Radioactive Material from a Nuclear Reactor," by the Committee on Protection against Ionizing Radiations.

Appendix K.—"Report on Emergency Exposure to External Radiation," by the Committee on Protection against Ionizing Radiations.

Appendix L.—"Comments on the Recommendations of the International Commission on Radiological Protection," by the Committee on Protection against Ionizing Radiations.

Reports of Societies

MANCHESTER MEDICAL SOCIETY

We report below two recent sectional meetings of the Manchester Medical Society.

Focal Chronic Pyelonephritis

On November 2 Dr. C. J. HODSON (University College Hospital, London) read a paper before the Section of Medicine on "Radiological Observations on the Natural History of Chronic Pyelonephritis." In it he considered the focal form of chronic pyelonephritis, which is commonly associated with uraemia when bilateral and with hypertension when unilateral. Dr. Hodson emphasized the close association of vesico-ureteric reflux with this condition. Now that reflux could be accurately diagnosed by radiological means it was possible to watch, for the first time, the formation and progress of these kidney lesions during life. Cases were shown of (*a*) pyelonephritis in a 3-months-old boy in which the affected part of a duplex kidney was subjected to reflux and in which very primitive renal tissue was found on section; (*b*) unilateral chronic pyelonephritis in children in which the kidney, having reached a certain size, showed no further growth over a five-year period, the opposite kidney undergoing marked hypertrophy; (*c*) a patient in whom a normal-sized kidney had undergone gross shrinkage after vesico-ureteric reflux caused by surgical interference with the lower end of the ureter. Dr. Hodson also produced other evidence to suggest that a kidney affected by pyelonephritis and reflux either did not grow or might undergo severe shrinkage. Cases of very small pyelonephritic kidneys might be examples of a failure of development in early life secondary to those two conditions, or their late result.

Tuberculous Adenitis

On November 8 Dr. H. B. ANDREWS presented to the Section of Surgery his results with 72 patients with tuberculous adenitis who had been treated at Wrightington Hospital, the regional centre for surgical tuberculosis, during the period 1949–58. There were 138 patients with supposed tuberculous lymphadenitis, 66 being pathologically unproved. Of the total, 57 required excision of tuberculous lymph-nodes. All patients were treated with a routine course of streptomycin, P.A.S., and isoniazid for four months under sanatorium conditions. The decision to excise was finally taken when there remained three weeks of anti-tuberculous therapy, any palpable affected lymph-nodes at that time being excised. Excision aimed at removing all affected lymph-nodes, which almost always proved to be more than were clinically apparent. All cases were of widespread lymphatic or haematogenous type, and the ages ranged from 10 to 60.

Of 43 patients in the age-group 10 to 29, six had recurrences after excision and two required further excision of other groups of nodes; four settled down on further treatment with anti-tuberculous drugs. In the remaining 14 cases in the age-group 30 to 60+, 11 excisions were successful; there was one recurrence which settled on further conservative regime, and there were two deaths from generalized tuberculosis several months after the excision.

The average follow-up time was three years, and 21 patients were discharged as "cured" after a five-year follow-up.

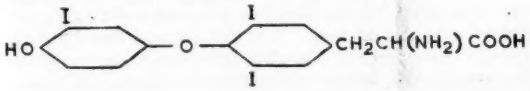
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Liothyronine ; L-triiodothyronine

"Cynomel" (Smith, Kline and French).
"Tertroxin" (Glaxo).

Chemistry.—This drug is the optically active, naturally occurring form of 3:5:3′—triiodothyronine, which has the following structural formula:



Physiology.—L-triiodothyronine is secreted together with thyroxine by the thyroid gland. Its biological action in stimulating metabolism is qualitatively similar to that of thyroxine, and weight for weight it is three to five times more active than the latter. Because it is more weakly bound to the serum proteins than thyroxine it enters the tissues more rapidly, and this probably accounts for the quicker onset and shorter duration of its effects.

Therapy.—L-triiodothyronine is used in the treatment of myxoedema coma, when it should be given intravenously in a dose of 100 μg., this dose being repeated, according to the response, at intervals of not less than four hours. It should, of course, be combined with other measures such as corticosteroid therapy and restoration of body temperature. Although triiodothyronine is probably the most potent drug available in the treatment of myxoedema coma, the condition is often irreversible, and the drug itself may produce dangerous cardiac complications.

In patients with thyroid carcinoma undergoing a course of treatment with radioactive iodine it is necessary to produce periods of hypothyroidism by withdrawing replacement therapy before giving the radioactive iodine. In such cases the period of disability due to hypothyroidism can be reduced by using triiodothyronine as replacement therapy.

It is also used in the diagnosis of suspected thyrotoxicosis, when the administration of 100 μg. daily for one week will suppress the uptake of radioactive iodine by the thyroid in the case of the normal gland and non-toxic goitre but not in the thyrotoxic gland.

The use of L-triiodothyronine in doses of 10 to 20 μg. daily, increasing gradually to 80 to 100 μg. daily, has been advocated in the treatment of primary hypothyroidism, but it would appear to have no special advantages over thyroxine in the treatment of this condition. Indeed, the less rapid effect of the latter is particularly desirable in the stage of control of the hypothyroidism in order to prevent the rising metabolic rate from outpacing cardiac adaptation. The drug may, however, have a place in a therapeutic trial of patients with doubtful hypothyroidism. A dose of 100 μg. daily in divided doses should be given ; a positive response will be evident within two or three days.

Claims that the drug is valuable as a "tonic" in the middle-aged female with non-specific symptoms of lassitude and tiredness have not been substantiated. Its use in assisting reduction of weight would appear to be equally irrational if a dose which will not produce side-effects is used.

Contraindications and Side-effects.—The drug should be given cautiously when patients have coronary artery disease or adrenal insufficiency. Angina pectoris may be induced in the hypothyroid patient. Overdose with the drug may produce tachycardia, nervousness, and excessive sweating together with other manifestations of the thyrotoxic state.

N.H.S. Basic Price.—Cynomel: 100 5-μg. tabs. for 4s. 5d. ; 100 25-μg. tabs. for 6s. 7d. Tertroxin: 50 5-μg. tabs. for 2s. ; 50 20-μg. tabs. for 2s. 7½d.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Falls in Old Age

SIR,—I have read Dr. J. H. Sheldon's article (December 10, p. 1685) with great interest ; but I am puzzled by his conclusion that "sensory defect (is) unlikely to play more than an adjuvant role" in responsibility for the falls of old people when, among the causes of accidents, the importance of "a deficit of visual signals" is found to be less only than mistaken belief that the bottom of the stairs has been reached—an error in which impaired vision often plays a part. Whilst I should not wish to question his explanation of the causes of the general insecurity of postural control and the liability to fall which are characteristic of old age, I should like to suggest that, among the many intriguing problems which remain to be investigated, the role of defective vision is an important one.

The causes of impaired vision in an ageing population such as ours are predominantly those of later years (86.2% of those registered blind in 1959 were over the age of 60), and, as ophthalmic surgeons are well aware, such defect frequently plays an important part in causing accidents—major and minor. Only a small proportion of the aged are segregated on account of this defect—if it is recognized and not tacitly accepted as an inevitable concomitant of old age—and it is clear from Dr. Sheldon's paper that defective vision may well have played a part in a large proportion of the accidental falls, if not in the Trips and the Vertigo groups. It appears to me unfortunate, therefore, that he should classify under the heading of poor illumination both defective vision, which calls for medical advice and is in many cases remediable, even in the old ; and a fault in the actual lighting which prompts quite different action.

Naked-eye or even ophthalmoscopic determination of the cause of impaired vision is possible only in a minority of cases ; but when the fact of its presence is assessable, as it is, with an accuracy possible in few other forms of sensory examination this disability should surely escape detection less frequently than it at present does. Our out-patient clinics and domiciliary visits become increasingly concerned with the problems of the aged in which the helpful approach suggested by Dr. Sheldon's paper is invaluable, and it is to be hoped that among these problems the major disability of impaired vision will not be overlooked.—I am, etc.,

London W.1. HENRY HOBBS.

Electrocardiographs in General Practice

SIR,—We have had an E.C.G. machine in our practice for two years, and would therefore like to answer some of Dr. John W. Wigg's queries (December 10, 1960, p. 1733). It is our opinion that an E.C.G. machine is one of the most helpful instruments one can have in general practice, and it is more than worth while for the benefit of patients and reducing the necessity of domiciliary consultations (and therefore saving our mutual income tax). Financially we cover the costs of running the machine, with a little bit over from the occasional private patient and issuing of reports, although in this practice private patients are not encouraged.

We decided to try an E.C.G. machine two years ago after a run of coronary thromboses which necessitated frequent

domiciliary consultations for diagnoses. An elderly machine was acquired—the motor traders would describe as a post-vintage thoroughbred—which, after we had used it for six months, developing our films in the evenings, made us decide it was worth while getting a new direct writer. These can be obtained for under £300. They are light and easily portable, are trouble-free in running, and no earth or external power supply is needed. The makers of our particular model, Philips Electrical Ltd., have given us courteous quick service whenever it has been required.

The interpretation of the results takes a little experience, and, speaking for myself, three months' evening reading of the textbooks gave me sufficient understanding to give some sort of opinion in tracings. I can recommend *Electrocardiography* by Wolff.[1]

Although the original reason for obtaining an E.C.G. machine was for coronary thromboses those cases are in fact a small percentage of tracings that we take, and we find a lot of uses for the machine that we never thought of at first—for example, we find the tracings helpful in telling us which of our hypertensive patients needs treating—we have found it useful for showing right ventricular strain in asthmatics and chronic bronchitics. We have found it useful for confirming heart lesions in our antenatal clinics. No opportunity has been lost in the past two years to take a tracing in any subject that warranted it for us to gain experience, so a lot of normal tracings have been taken. This will, we think, benefit us very much in the future as we will have a library of tracings of all our known hypertensive patients, so that any change we can treat accordingly.

The other benefits which must be mentioned are psychological both for the patient and for us. An overworked business executive worrying about his heart will not be satisfied unless an E.C.G. is done. I think myself that it is our job to do this and reassure him rather than continued reference to specialists.

Some of our colleagues have said that they would not have time to use an E.C.G. machine, but we maintain that we can take a tracing quicker than we can syringe an ear, and that with cutting down the domiciliary consultations time is in fact saved. We now both of us feel that we could not do without our machine, an average of two E.C.G.s are taken a week by us, and it is our practice to show the tracings to each other without any clinical details as a form of mental exercise, which makes the time when one is having coffee in the morning pass pleasantly. We have of course had to refer patients and tracings for second opinions, and we have found our consultants more than helpful in interpreting our results and teaching us how to read them.—I am, etc.,

Botley. J. H. B. URMSTON.

REFERENCE

[1] Wolff, Louis, *Electrocardiography: Fundamentals and Clinical Application*, 2nd ed., 1956. Saunders, Philadelphia.

SIR,—In reply to Dr. John W. Wigg (December 10, p. 1733) the general practitioners working in our Health Centre were of the opinion that the original cost of a direct-writing cardiograph at £300 was excessive although maintenance costs would be very small. Most G.P.s felt they would be unable to read the recordings and in the majority of cases would need the guidance of the consultant.

The local authority, however, said that should doctors not using the Health Centre wish to have E.C.G. facilities they would be willing to allocate a room in the Health Centre and provide the necessary equipment. At the moment the matter is shelved until discussion at the next house committee meeting.—I am, etc.,

Alderman J. Cohen Health Centre, Springwell, Sunderland. HENRY F. GOLDMAN.

SIR,—The question asked by Dr. John W. Wigg (December 10, p. 1733) on the use of cardiography was bound to arise and has probably already arisen in other areas when health centres were contemplated. Like Dr. Wigg, I should also be interested in hearing of the experiences of others who make use of the E.C.G. in their practices, especially as I have undertaken to make an assessment of just this particular problem for the College of General Practitioners. It is understandable that the well-trained practitioner of to-day wishes to make use of every modern device in diagnosis, for the benefit of his patients, and already notes with satisfaction that most of the hospital diagnostic facilities are openly available to him. It is also natural that he may wish to make part of his own equipment any technical aids with which he was made familiar during his training, if they are at all adaptable for use in general practice. No doubt the stethoscope, the sphygmomanometer, and the ophthalmoscope all went through this gradual assimilation into general practice, and from being thought an expensive and unnecessary luxury, dangerous in the hands of the uninitiated, soon became a *sine qua non*.

I use a Cambridge Transrite (Mk. II) battery instrument, which is trouble-free and will stand a lot of rough treatment (one was taken on the Everest expedition), and I took a hundred graphs before the batteries needed renewing: so the maintenance cost is negligible. It is the initial outlay (although there is a tax allowance for new equipment) and the time factor which make your correspondent wonder whether they are worth while even under the more favourable conditions of a health centre. I find it takes twenty minutes to take a record from the moment of setting up to shutting the box again; that its use is easily accepted by patients, most of whom are extraordinarily familiar with what doctors are expected to do these days. I find that the use of the E.C.G. lessens the number of references to hospital and sometimes avoids it altogether. However infrequent are the cases, when it proves a short cut to diagnosis, as when one can graph a transient disorder of rhythm or confirm an infarction where the physical signs and symptoms were so equivocal that one was prepared to dismiss the case as non-cardiac—when it does, it is worth its weight in gold. The majority of cases in general practice afford such opportunity for serial clinical observation that the E.C.G. record contributes nothing at all, or at the most only confirms what was obvious, but even then it is something to have written evidence to refer to when the patient's physical signs have disappeared or for later discussion with a specialist. On the whole, the resulting improved standards of diagnosis probably outweigh any savings effected on other branches of the Health Service.

It is said that the cardiograph has reached the limit of its usefulness, and cardiac centres now turn to more technical and specialized means of investigation; but if the cardiograph is now a routine check, the G.P. cannot expect open facilities as in an *x*-ray department. Interpretation of the E.C.G. is too difficult to be attempted without seeing, or at least knowing a lot about, the patient, and unless the G.P. is prepared to read his own graphs he should refer the patient to a consultant. The G.P. will need to refer a number of records to a consultant, in any case, depending on his familiarity with the subject, but I believe with practice and brushing up his basic knowledge he should be able to interpret the majority.—I am, etc.,

Stockton Heath. R. GUEST GORNALL.

SIR,—May I crave your indulgence to reply to Dr. John W. Wigg (December 10, p. 1733) on the use of the E.C.G. in general practice? It is two months since I

bought the latest Cambridge Transrite electrocardiograph, and have enjoyed immensely my work with it. In detail my answers to his specific questions are as follows:

(1) One does not need to be working in a "centre" to find the benefit of this work. We are two in a partnership here, and although my partner leaves interpretation to me he is learning how to work the instrument so that he can go to a case and bring away the tracing without calling me out.

(2) Do they find them worth while? Yes.

(3) Are they expensive to maintain? The original cost is £275. After that, rolls of paper, tubes of jelly, replacement batteries, etc., are a matter of only shillings a month.

(4) Do they wear out quickly? No.

(5) Savings to other branches of the N.H.S.? The answer here surely is that all these patients would be saved the trouble of referral to hospital and hospital costs thereby reduced.

(6) How often do they need consultant opinion on tracings? So far, not at all (see below).

(7) Can a G.P. learn to interpret the majority? This depends on the G.P. and is really the crux of the problem. Before buying my instrument I had three months' postgraduate instruction in Edinburgh and took the M.R.C.P. (failed, of course). Then I studied for three or four months from the textbook. This is perhaps the only consultant field in which *all* the work can be done from this source. It is very important, in my view, to concentrate at first on the basic physics and physiology (with a dash of anatomy). Any G.P. who hopes to learn to interpret tracings by rule of thumb—that is, by trying to correlate a certain shape of tracing with a certain condition—is doomed to frustration and wasted effort and money. It is essential that as one's eye runs over the tracing a certain pattern of electrical events must be in the background all the time. Wolff's *Electrocardiography* is a difficult book, but to attempt interpretation of E.C.G.s without making oneself its complete master would lead one into a very high incidence of false positives and missed diagnoses. Recently a number of consultants were asked to give an opinion on a number of E.C.G.s. There was a considerable discrepancy between the opinions of different consultants on a given tracing and even a difference in the opinion of a given consultant on the same tracing at different times. The answer to this one, of course, is that the E.C.G. is to be judged, like an *x*-ray, only in relation to the rest of the picture. In this regard the G.P. should be in a more advantageous position than the consultant, assuming he has a reasonable knowledge of cardiology and has access to other means of investigation—for example, *x*-rays. If any G.P. thinks that by obtaining an E.C.G. machine he can obtain a short-cut to cardiological diagnosis, he is doomed to disappointment.

These conditions given, I would say that this work is most rewarding, most stimulating in keeping one's standards at the highest level both in cardiology and in every other field, for one finds that excellence in one field demands similar standards all round.—I am, etc.,

Great Glen, Leicestershire. G. A. STANTON.

REFERENCE

1 Wolff, Louis, *Electrocardiography: Fundamentals and Clinical Application*, 2nd ed., 1956. Saunders, Philadelphia.

Arteritis

SIR,—The article by Drs. J. W. Paulley and J. P. Hughes (November 26, p. 1562) is of considerable value in that it draws attention to the importance of arteritis as a cause of many syndromes. The nomenclature is, however, confusing, as in many cases no giant-cell formation can be demonstrated, and, as the authors say, the condition is not confined to the aged, though it is more common in the elderly. In 1946 Gibson, Kersley, and Desmarais[1] described the widespread arteritis in the muscles in rheumatoid arthritis, and in 1951 I described[2] the syndrome of muscular pain, raised sedimentation rate, and wasting in the elderly after stress, and attributed it to a rheumatoid-like condition. Rest and, if necessary, A.C.T.H. or steroids were advocated. Excessive fatigue was the commonest trigger factor in our series, with psychological trauma, as suggested by Dr. Paulley, taking second place. The prognosis was moderately good on removal of the trauma. A.C.T.H. was easier to withdraw than steroids when either was necessary. In 1953 Bagratuni published his description of this anarthritic syndrome.[3]

In the cranial form all clinicians have seen many gradations from "temporal arteritis" to an anarthritic and sometimes an arthritic "rheumatoid" syndrome, usually in the elderly. Headache with raised sedimentation rate is a frequent type of onset, with blindness or diplopia following if treatment is not adequate. The myalgia tends to follow and be very persistent. Do not these two syndromes stem from the same source as many others, and are they not merely manifestations of a much more deeply situated process—perhaps associated with auto-immunology or at least some abnormality of antibody formation, resulting from the effect of stress on some biochemical weakness? Is it not better to consider these conditions of arteritis as just syndromes rather than suggest that they are actual entities?—I am, etc.,

Bath. G. D. KERSLEY.

REFERENCES

1 Gibson, H. J., Kersley, G. D., and Desmarais, M. L., *Ann. rheum. Dis.*, 1946, **5**, 131.
2 Kersley, G. D., *Report of Second European Congress of Rheumatology*, 1951, p. 388. Editorial Scientia, Barcelona.
3 Bagratuni, L., *Ann. rheum. Dis.*, 1953, **12**, 98.

Status Asthmaticus Treated by Hypnosis

SIR,—I have been interested in the history of Dr. A. H. C. Sinclair-Gieben's asthmatic patient who died after hypnosis (December 3, p. 1651), and would like to make an additional comment.

Sudden death is not unknown in asthma, quite apart from status asthmaticus. I described a small series of cases in 1955, and I attempted to discover a means of detecting patients to whom this disaster was liable to happen. Three significant features were found: The only common factor in every case was a profound emotional disturbance which had a clear relation to the onset of asthma. The usual methods of treatment were found to be quite ineffective in every case. The most significant feature was the attitude of the patient to his illness. The average asthmatic learns to adjust himself and to live with the complaint. In this particular group the usual attitude was one of *panic*, which was noticeable even in anticipation of an attack.

The conclusion was that, when an asthmatic patient is found to exhibit this panic reaction, great care should be taken in expressing a prognosis. Of course, sudden death in asthma may be due to common drugs. Of these by far the most dangerous is aspirin.—I am, etc.,

London N.W.1. JAMES MAXWELL.

REFERENCE

1 Maxwell, J., *Brit. J. Tuberc.*, 1955, **27**, 208.

SIR,—I was interested to read the article by Dr. A. H. C. Sinclair-Gieben entitled "Treatment of Status Asthmaticus by Hypnosis" (December 3, p. 1651). One cannot, however, study this case without making certain

observations. The most remarkable fact of the case comes in the "Final Note," which states, "A few days after discharge the patient died suddenly of acute heart failure."

In recent years there has, quite rightly, been a new awareness amongst the profession of the values of hypnosis in treatment. It is quite obvious that the patient most probably would have died of his status asthmaticus without the use of hypnosis, all other known methods having been tried without avail. Asthma must be considered, however, as a symptom and not a disease. What were the true psycho-dynamics of this patient's asthma? According to Dr. Sinclair-Gieben he was a very well adjusted man. This, with due deference, I question. I am certain that by careful analytical questioning one would find gross emotional upset.

This asthmatic attack was the patient's unconscious means of dying. When the attack was cured he unconsciously realized that this way of escape had been removed, and so three days later he dies of acute heart failure. This case emphasizes that when treating cases of asthma by hypnosis one must endeavour to find the true unconscious meaning of the attacks. In no way am I suggesting that the use of hypnosis in this case led to the patient's death, but I am endeavouring to bring to the notice of all who use hypnosis in the treatment of asthma the tremendous importance of ascertaining a history of its deep-seated dynamics. Unless this precaution is taken other alarming symptoms from time to time will reveal themselves.—I am, etc.,

London W.1. ALAN AKEROYD.

Is Thalidomide to Blame?

SIR,—I feel that four cases which have occurred in my practice recently are worthy of mention, as they may correspond to the experience of other practitioners. They all presented in more or less the same way—each patient complaining of: (1) Marked paraesthesia affecting first the feet and subsequently the hands. (2) Coldness of the extremities and marked pallor of the toes and fingers on exposure to even moderately cold conditions. (3) Occasional slight ataxia. (4) Nocturnal cramp in the leg muscles. Clinical examination in each case has been essentially negative, and during this time I have not noticed similar cases in my practice.

It seemed to me to be significant that each patient had been receiving thalidomide ("distaval") in a dose of 100 mg. at night, the period during which the drug had been given varying from eighteen months to over two years. Thalidomide is generally regarded as being remarkably free of toxic effects, but in this instance the drug was stopped. Three of the patients have now received no thalidomide for two to three months, and there has been a marked improvement in their symptoms, but they are still present. The fourth patient stopped taking the drug two weeks ago, and it is therefore too early to assess the effect of withdrawal.

It would appear that these symptoms could possibly be a toxic effect of thalidomide. I have seen no record of similar effects with this drug, and I feel it would be of interest to learn whether any of your readers have observed these effects after long-term treatment with the drug. I might add that I have found it otherwise to be a most effective hypnotic with no "morning hangover" effect. It has been especially useful in patients with skin pruritus and discomfort.—I am, etc.,

Turriff, Aberdeenshire. A. LESLIE FLORENCE.

Digitalis Poisoning

SIR,—Your contributors (November 12, pp. 1402 and 1409) are to be congratulated on drawing attention to atrial tachycardia with block as a manifestation of digitalis intoxication. Since reading Lown and Levine's description[1] of this five years ago I have noted several examples, one of which has been published elsewhere.[2]

Perhaps the rather confusing terminology prevents wider recognition. "Paroxysmal," although used by Levine, is not a label that can be given as a result of a single cardiographic study, and seems inappropriate when each "paroxysm" is drug-induced. And surely the time has come to stop trying to make a rigid distinction between atrial tachycardia and flutter which Prinzmetal[3] has shown to be essentially the same phenomenon, differing mainly in the rate of discharge of an ectopic focus.

The important point, as Dr. Samuel Oram and his colleagues say (p. 1402), is recognition of the rapid atrial rhythm which is due to digitalis. The curious variability of the auriculo-ventricular block is one of its most suspicious features.—I am, etc.,

St. Helier Hospital, Carshalton, Surrey. C. P. PETCH.

REFERENCES

[1] Lown, B., and Levine, S. A., *Current Concepts in Digitalis Therapy*, 1955. Churchill, London.
[2] Petch, C. P., *Brit. J. clin. Pract.*, 1959, **13**, 266.
[3] Prinzmetal, M., *et al.*, *The Auricular Arrhythmias*, 1952, 3rd edition. Thomas, Springfield, Illinois.

A Case of Atrial Septal Defect

SIR,—I read with great interest the discussion between Professor J. McMichael and Dr. Monica Bishop about the evidence of carditis in a case of atrial septal defect (November 26, p. 1585), as I happen to be working (with Professor R. Scalabrino) on a very similar instance of Lutembacher's syndrome: a 44-year-old woman, with a story of heart disease, cardiogram showing right bundle branch block and right ventricular hypertrophy, who died from cardiac failure and at whose necropsy a 3.5-cm. wide atrial septal defect, mitral stenosis, and tricuspidal lesions were found. Following on serial sections of the His–Tawara bundle, I noticed several round-cell aggregates, fibrosis, and thick-walled, stenotic arteriolae at the upper portion of the ventricular septum. The bifurcation and the right branching of the bundle seemed to be involved and damaged. The base of the tricuspid, the walls of the right atrium, and the region of the sinus node showed groups of lympho-histioid elements. No typical Aschoff bodies, however, have been observed.

I would like to point out that such a carditis in Lutembacher's syndrome could be regarded as not uncommon and, sometimes, as responsible for clinico-pathological changes (conduction troubles) besides the classic valvular ones.—I am, etc.,

Department of Pathology, University of Milan. LINO ROSSI.

Chemical Diagnosis of Steatorrhoea

SIR,—Although the facts about steatorrhoea determined by Dr. Edward B. Hendry (October 1, p. 975) are mostly unexceptionable, the conclusions are quite misleading. He finds, as do most other investigators, that the 24-hour faecal output of fat is a very reliable method of diagnosing steatorrhoea, whereas values of per cent. of fat in dried stool correlate very

poorly. The only new criterion he proposes is that fat contents less than 10% (or possibly 14%) of dried stool can be eliminated from consideration of steatorrhoea. In his series he states that the procedure would have eliminated 92/231 (40%) of the 24-hour fat analyses.

Now, in the first place, he did not, in fact, do random stool specimens for his screening test, but determined per cent. fat excretions on an aliquot of the complete 24-hour specimen from a prepared patient. We have no way of knowing that his results would have been comparable had he actually used random specimens on out-patients. Secondly, other investigators do not seem to find such a relatively large number of patients with percentage fat below 10% or 14%, and this finding may be due to a local peculiarity. Thirdly, the proposed procedure, far from simplifying the work of the laboratory, increases it greatly. This is because 24-hour stool fats can be determined on wet stool by the methods of Van de Kamer *et al.*[1] with about one-third the effort (and about one-tenth the unpleasantness) required for determination of percentage fat in dried stool. In order to eliminate 92 simple wet stool analyses, therefore, the author has undertaken 231 tedious dry stool analyses—hardly a saving in labour.

Finally, I would recommend to your readers a screening procedure which is much simpler than either of the above: the serum carotene. A serum carotene above 70 μg./100 ml. effectively rules out steatorrhoea. Perhaps some 70% of patients would be ruled out by this simple test, leaving 30% who could be diagnosed by a 24-hour fat excretion (on wet stool). The one point that Dr. Hendry has shown clearly (as have others[2]) is that relatively simple preparation of the patient gives an entirely reliable 24-hour fat excretion.—I am, etc.,

Royal Columbian Hospital, New Westminster, B.C., Canada. RALPH SPITZER.

REFERENCES

[1] Van de Kamer, J. H., in *Standard Methods of Clinical Chemistry*, Vol. 2, 1958, ed. D. Seligson. Academic Press, New York.
[2] Cooke, W. T., *Brit. med. J.*, 1958, **2**, 261.

Smallpox in Nyasaland

SIR,—In the letter from the British Medical Association in Nyasaland (December 24, p. 1882) it is written that, in a statement to the press in London, a member of the Association denied the existence of an outbreak of smallpox in Nyasaland. The letter also states that the Nyasaland B.M.A. believes that the figures issued by the Director of Medical Services (Nyasaland) are accurate.

It should be pointed out that the member referred to did not deny the existence of an outbreak, but denied the existence of an epidemic. I do not wish to begin a correspondence on the difference between an outbreak and an epidemic, but it should be pointed out also that the D.M.S. has not used the word epidemic, but refers to a "serious outbreak." There is thus no incompatibility between the statement of the said member and the Director of Medical Services.

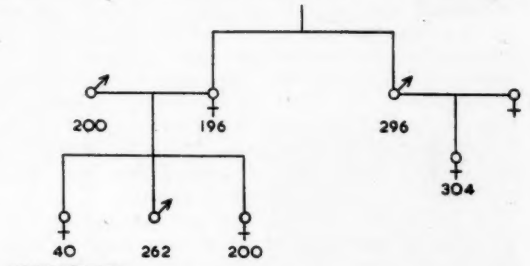
It is extremely important that any statement made by the B.M.A. in Nyasaland should be accurate, especially at the present time, as such statements are being used by the press as political propaganda, and we do not wish to discredit our profession.—I am, etc.,

Mlanje Mission, Nyasaland. KATHERINE M. ROBERTSON.

Suxamethonium Apnoea in Infancy

SIR,—Writing under the above heading (August 13, p. 535), Drs. L. Kaufman and H. Lehmann, and Mrs. Elsie Silk produce a family tree showing low pseudocholinesterase levels in the propositus and two siblings. It is therefore presumably the intention of these authors to suggest some genetic scheme of inheritance of this characteristic, though they produce no evidence for such an assertion.

I recently encountered a case of suxamethonium apnoea with low pseudocholinesterase, and, in the light



of the statements of Kaufman *et al.*, I decided to investigate the family tree. The result was as follows, being expressed in units=mols/ml./hour=mols of acetylcholine destroyed by 1 ml. serum in one hour. (Normal limits: 130–320.)

These results lend no support to the suggestion of any genetic behaviour on the part of pseudocholinesterase deficiency.

I am indebted to Mr. E. B. Love, B.Sc., F.R.I.C., and Mr. V. Rich, F.I.M.L.T., for the biochemical work involved.
—I am, etc.,

Swansea General Hospital. F. D. ADRIANVALA.

Uterine Rupture after Oxytocin

SIR,—To those who still advocate and practise medical induction I would respectfully suggest that they read Donald's *Practical Obstetric Problems*, second edition, Chapter XV.[1] "It is a common practice to prescribe castor oil, hot bath, and enema as a test of maturity in the mistaken belief that it is totally harmless. If the patient, as often happens after a hectic few hours of excretory activity, fails to go into labour, the psychological effects may be profound." Disappointment, fear for her baby, fear for herself, etc. In my opinion, it is on account of the usual failure to "bring on" labour that medical induction is so dangerous, because it stimulates some of the more enthusiastic and ill-advised "interferers" to give repeated intramuscular injections of oxytocin—a practice completely condemned by Wrigley at the Congress meeting at Cardiff in July, 1959, and one which can cause such a tragic result, as in the case reported by Dr. P. J. Dwyer (November 26, p. 1570).

This unfortunate young woman had had two previous normal confinements—and presumably the only reason for the "full" medical induction was because she was supposed to be one week overdue. Many obstetricians are undecided as to the importance of post-maturity and the need for induction, but I doubt if any obstetrician is able to decide that any pregnant woman is one week overdue. After nearly 40 years in the practice of

midwifery, both as G.P. and consultant, I would say that there are still too many problems in obstetrics, without adding to them by "full medical induction" for any pregnant woman.—I am, etc.,

Bury St. Edmunds, Suffolk. D. J. P. O'MEARA.

REFERENCE

[1] Donald, I., *Practical Obstetric Problems*, 2nd ed., 1959. Lloyd-Luke, London.

Anaesthetizing the Nose

SIR,—The nose is usually anaesthetized by spraying, by packing with ribbon gauze, or by applying the local anaesthetic agent on orange-sticks. Moffett[1] pointed out that these methods are not always satisfactory and proposed running the solution into the nose with the head in different positions. His method has a number of advantages, but takes 30 minutes to complete; it requires a lot of co-operation and some agility on the part of the patient, and a special needle for introducing the fluid. The following method has the same advantages but is quicker and simpler.

An appropriate dose (say 0.5 g. lignocaine) of local anaesthetic is made up in 40 ml. of warm water, to which 0.5 ml. adrenaline hydrochloride, B.P., may be added (1:80,000). Two pillows are placed under the patient's shoulders as he lies on a couch or operating table, so that his head hangs over them with the neck fully extended, the chin vertically above the external auditory meatus. The administrator sits at his head and instructs the patient to breathe through his mouth. Half the solution is now put in a medicine glass or syringe and poured into one nostril until it is full (see picture). As the level of the fluid reaches the external nares the patient may try to swallow, indicating that it has reached the soft palate at the back of the nose. The patient is reassured that this will not interfere with his breathing freely through his mouth and a firm hand on his forehead will prevent him involuntarily tipping the fluid into his pharynx. The second nostril is now filled and the nose held closed with finger and thumb to prevent him breathing through it. After three minutes the patient is given a swab in his right hand, sat up, and told to blow his nose and spit out any fluid in his throat. The quantity of fluid required varies greatly, as does the quantity recovered by the final manœuvre. The entire mucosa of the nose will now remain anaesthetized for an hour or more. Other solutions besides anaesthetics may, of course, be applied to the nasal mucosa in the same way.

This method has been used over the past five years in about one hundred operations for submucous resection of the nose with complete satisfaction. Moffett claims four advantages for instilling a local anaesthetic solution into the nose: (1) The maximum quantity of drug used is known; (2) instillation is effective when the anatomy is abnormal; (3) no particular skill is required; and (4) the procedure is not painful. The present method has three further advantages: (1) It only takes three minutes; (2) no movement of the patient is necessary once he is in position; and (3) no special apparatus is required.—We are, etc.,

Hillingdon Hospital, Uxbridge, Middlesex. R. I. BODMAN. F. BOYES-KORKIS.

REFERENCE

[1] Moffett, A. J., *Anaesthesia*, 1946, **1**, 31.

Hereditary Spherocytosis

SIR,—The results of Dr. A. C. Allison and his colleagues (December 17, 1960, p. 1766) on the analyses of phosphatides in the cells of hereditary spherocytosis are interesting. Three years ago I and my colleagues made similar analyses by the same chromatographic methods on six patients with this disease, and were unable to find any statistical differences between the component phosphatides of their red cells and those of normals. Dr. Allison and his colleagues do not give the separate results for each of the two patients whom they studied. It would be surprising to me if these were similar, since one of the two patients had had a splenectomy, and a consequence of this would be a difference in the mean ages of the two individuals' cell populations. It is, of course, known that the lipid content of red cells varies with cell age.

There are other difficulties to me in accepting their hypothesis of a causal relationship between the lysophosphatide content and the shape of the red cells as the primary genetical defect in this disease. In hereditary spherocytosis cell shape may vary from extreme spherocytosis to none detectable at all, yet in these two extreme states the haemolytic rates in the individuals may not differ. Furthermore, it has now been shown that the shape of hereditary spherocytic cells can be reverted towards normal by inducing a state of iron deficiency in affected individuals, but this does not alter the haemolytic rate. These findings suggest that any structural changes in red cells would not influence their vulnerability through altering their shape. I hope the authors will make further observations on a greater number of hereditary spherocytics, particularly selecting some with differing cell shape.—I am, etc.,

T. A. J. PRANKERD.

University College Hospital Medical School, London W.C.1.

White Mouse Medicine

SIR,—As a naturalist, I noted a mass-scale experiment in fat-deprivation between 1940 and 1950. During this period, particularly over the middle years and in western London and the Thames Valley, a large section of the populace were deprived of animal fats as thoroughly as a benevolent government could manage it. The principal beneficiaries of the experiment were elderly to middle-aged "white-collar workers"—such lower forms of life as clergymen, lawyers, doctors, schoolmasters and mistresses, and other under-privileged persons.

I had been working as a surgeon in London ever since I left the Army in 1920. I knew that there was such a thing as coronary disease, but I regarded it as a prerogative of the aged, and not a usual thing at that. As a student I had hardly heard of it—and my masters were Clifford Allbutt and Archibald Garrod. Until the war years it had made no impact on me as something that would kill or cripple friends and colleagues, often many years junior to me. For the moment I was a little startled to read "epidemic" in the letter of Dr. R. Mackarness (December 10, p. 1737), but looking

back on that period I remember my wife coming in again and again from meetings of the Medical Benevolent Fund with news of another young doctor who had died of coronary disease at an age to leave children, themselves of school age. This is a casual observation and impossible to support by statistics. But it deserves some comment. Of all people who went short of fats at that time, young and middle-aged doctors were prominent "white mice."

On general principles I heartily agree with Dr. R. W. Cockshut (December 10, p. 1738). Life is really getting too dangerous to live. La Rochefoucauld remarked about three hundred years ago that "the living strictly by rule for the preservation of health, is one of the most troublesome diseases that can be." The prospect of dragging out my remaining years on a diet of brown bread, whisky, and cod seems to me "*propter vitam vivendi perdere causas.*"—I am, etc.,

London S.W.1. F. W. WATKYN-THOMAS.

Clients of Prostitutes

SIR,—I read your leading article on the above subject (December 17, p. 1794) with great interest. I do not think it is sufficiently appreciated that men who resort to prostitutes have not advanced beyond the adolescent "fantasy level" of sexual stimulation—which, of course, means that sexual desires are continually being whipped up by means of fantasy-thinking. Prostitutes, of course, realize this and endeavour to play their part in this fantasy world, a part which wives, as a rule, refuse to play, with the result that such men are frequently impotent with their wives, or have so outraged them that all intimacy between them has long since ceased. In the sexually matured man, sexual desire is integrated with and completely based upon the tender emotions, and is, as a consequence, infinitely more stable. In the absence of the expression of these emotions, the sexual life is left alone and comes to no harm.

Nor do I think it is sufficiently appreciated what a delicate plant the sexual instinct is and how easily it can be killed. Almost all prostitutes, of course, are completely frigid—view men who resort to them with loathing—but continue in the life for various characterological and economic reasons. And, of course, the promiscuous man or women faces similar dangers from the way they use their sexual instinct. Sex expression divorced from the tender emotions is, as a rule, most unstable and most unsatisfying, and nearly all such men and women soon exhibit varying degrees of impotence or frigidity. It is the appearance of the latter which often drives these people to greater promiscuity, in the hope of achieving the sex union of their fantasy—a hope rarely fulfilled. And more tragically in the case of men, as I have seen, the unsatisfied sexual fantasy life may shift from prostitutes to criminal assaults on children. —I am, etc.,

Pinner. ROBERT THOMPSON.

Surgery of Appearance

SIR,—Fig. 3 in the article by Mr. Patrick Clarkson and Dr. David Stafford-Clark (December 17, p. 1768) shows, to my mind, not only a girl with underdeveloped breasts but also a girl with overdeveloped shoulders. Was any effort, in fact, made to assess the state of this girl's endocrine glands? Might not hormone therapy have cured her, where plastic surgery has only helped? I should very much like to know.—I am, etc.,

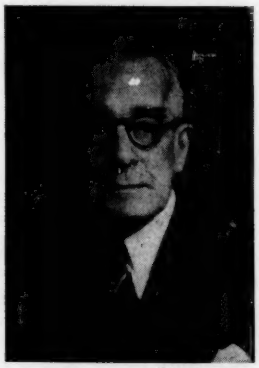
London N.W.4. T. C. DANN.

Obituary

Sir ERNEST FINCH, M.D., D.Sc., M.S., F.R.C.S.
Hon.F.R.C.S.I.

Sir Ernest Finch, honorary lecturer on the history of medicine and formerly professor of surgery in the University of Sheffield, and a former vice-president of the Royal College of Surgeons, died on December 16 at the age of 76. For many years the leading surgeon in Sheffield, he was admired throughout the surgical world for his personal qualities and respected for his learning, experience, and devotion to his specialty.

Ernest Frederick Finch was born on September 2, 1884, and educated at the Commercial Travellers' Schools, Hatch End, near London. Gaining a scholarship to the University College of Sheffield in 1901, he graduated M.B., B.S. (with honours in pathology) at the University of London in 1906. For a year before this he had been working as a demonstrator of physiology in Sheffield, and had published papers in the *Transactions* of the Physiological Society. In 1908 he was granted the degrees of M.B., Ch.B. (*ad eundem*) by the new University of Sheffield. Proceeding M.D.(London) in 1909, he took the F.R.C.S. in 1911 and the degree of M.S. (London) in 1913. From 1907 to 1912 he was casualty officer, house-surgeon in various departments, and surgical registrar at Sheffield Royal Infirmary, to the staff of which he was elected in 1912 as honorary assistant surgeon. He also held the posts of demonstrator of applied anatomy and surgical pathology in the university.



[*Elliott and Fry*

During the first world war he served as a major in the R.A.M.C., first in France with the 3rd West Riding Field Ambulance (T.F.) and later with the 3rd Northern General Hospital. On his return to civilian life he joined the senior staff of his own famous teaching hospital in Sheffield, where by his skill, hard work, and attractive personality he soon made a great reputation and built up a large practice. From 1933 to 1944 he was professor of surgery in the university, and when he ceased to lecture on surgery he was appointed honorary lecturer on the history of medicine. On his retirement from the active staff of the Royal Infirmary he was appointed consulting surgeon, and, by the aid of subscriptions from his colleagues and former students, the Ernest Finch Medical Library was established in the Royal Infirmary. For the great work which he had done in Sheffield he was in 1951 honoured with a knighthood. In Sheffield itself his distinction as surgeon and citizen was recognized by his being elected a Trustee of the Sheffield Town Trust, and in 1953 the university conferred on him the honorary degree of D.Sc.

Sir Ernest Finch devoted much time to the work of the Royal College of Surgeons, on the council of which he served from 1941 to 1954. Elected a vice-president in 1949, he acted as senior vice-president in the following year. He delivered the Bradshaw lecture in 1951, the Vicary lecture in 1953, and in 1957 he gave the Hunterian oration, taking as his subject "The Influence of the Hunters on Medical Education." Before the Medical Society of London he gave the Lettsomian lectures in 1947, his subject being "Cancer, Yesterday, To-day, and To-morrow." He held many offices in medical organizations. He was a former president of the Association of Surgeons of Great Britain and Ireland,

of the Section of Surgery at the Royal Society of Medicine, and of the Sheffield Medico-Chirurgical Society. Chairman of the Sheffield Division of the B.M.A. in 1933–4, he was a vice-president of the Section of Surgery at the Annual Meeting in 1952; and he also served for a time on the Association's Evidence and Negotiating Committees before the advent of the National Health Service. A member of the Sheffield Regional Hospital Board, he served on the Standing Cancer and Radiotherapy Advisory Committee from its inception in 1949. For the General Medical Council he was a Visitor of Medical Schools and an Inspector of Final Examinations.

Sir Ernest Finch was a skilful surgeon and a friendly and companionable man. He was a member and former president of the Moynihan Surgical Club, and his popularity can be judged by the fact that he acted as secretary to that exclusive club for 21 years, and he wrote an interesting history of it. Two years ago he was elected an Honorary Fellow of the Royal College of Surgeons in Ireland. Of average height and rather slender build, he had a soft voice and a pleasing manner, and he had hosts of friends. A witty speaker and raconteur, he could tell a good story in a broad Yorkshire dialect. He was a good committee-man, a wise counsellor, and a faithful friend.

In 1912 he married Mary Ainsworth, and she and a son of the marriage survive him.

A. G. Y. writes: Sir Ernest Finch was the doyen of the profession in Sheffield. For many years he carried on an extensive private practice as a consulting surgeon, lectured at the university on clinical surgery, and was a very popular clinical teacher. He rendered great and valuable service to the cause of medical education, was full of constructive ideas, and helped materially in the building up of the Sheffield Medical School. He examined for the Fellowship of the Royal College of Surgeons and was an external examiner in surgery to a number of universities. He visited, in an official capacity, many of our medical schools and thus acquired a comprehensive knowledge of medical education in Britain.

Another of his great interests was the history of medicine. He gave many addresses on the subject, and there can be no doubt that he derived great inspiration from his study of the lives of the great doctors of the past. Blessed with a most retentive memory, he never forgot his old students and corresponded with many of them. He was greatly loved and respected by his younger colleagues and never missed an opportunity to do them a service.

Sir Ernest Finch was a great surgeon, but always humble and approachable, and he looked upon his wide knowledge and experiences of surgery as well as upon the honours which were showered upon him primarily as the means of giving better service to his fellow men. He was a friend of no mean order and showed a lively interest in the welfare of his colleagues right up to the last.

W. D. writes from Dublin: The news of the passing of Sir Ernest Finch has caused widespread regret amongst his colleagues in Ireland, where he was known not merely as one of England's leading surgeons but as a friend to many individual practitioners in the fields of medicine and surgery. From his many visits during the past 40 years he knew this country more intimately than could any of his colleagues on the other side of the Irish Sea. He had come to us first in 1925 for the meeting of the Association of Surgeons of Britain and Ireland held in Dublin under the presidency of Sir William Taylor, a visit repeated in 1949 under the presidency of the late Harry Meade. As the honorary secretary of the Moynihan Travelling Club for more than twenty years, with its alternating visits to surgical centres at home and abroad, he had come to us with a Ulysses-like acquaintance with the surgical leaders of two continents.

In 1952, by invitation of the Irish Medical Association, he attended our Annual General Meeting held in Waterford, sailing on a sunny morning of July up the estuary of the river Suir as he stood like a Viking of old beside the skipper on the bridge, before coming ashore beneath Reginald's Tower. Down there in Munster he has left an imperishable memory, evoked by his manner of arrival, his simple *bonhomie*, his address to the assembled members, for the most part general practitioners, whose difficulties he compared with those he had come to know amongst their confrères among the Yorkshire moors. His after-dinner speech that evening is still talked of by many who were there to hear it delivered. In subsequent years he came back as extern examiner in surgery to the National University of Ireland, with its constituent Colleges at Galway, Cork, and Dublin, and within the past five years as Visitor for the General Medical Council. On every visit he gained an ever-widening acquaintance with Irish surgeons, and a sympathetic appreciation of the work they had to carry out, often under difficult handicaps.

For Finch's outstanding quality, revealed in all these visits, was his desire to help rather than to criticize; with the wisdom of a Cicero he knew that it is often of more consequence to act considerately than to think too wisely. When criticism was forthcoming it was gently delivered, never *cassant*: the most tolerant of men, dogmatic assertion was repellent alike to his intelligence and his character. As an after-dinner speaker he shone: his gift of humour, that "light divine of human mind," displayed the merry heart that goes all the day, and the *savoir-faire* that knows the importance when offering an opinion or a judgment of not being too serious.

The greatest trust between man and man, said Bacon, is the trust of giving counsel. Morley described John Stuart Mill as a "great and benignant lamp of wisdom," a description fitting Ernest Finch's wise assistance given to so many in this island struggling with the difficulties and the hurdles of medical education, and grievous is it that his lamp should be extinguished even in the fulness of time. His wide knowledge of men and events, his clearness of mind, and sympathy of heart have been, and still remain to-day, the inspiration of all who have benefited by his counsel. To all who sought him he was a most lovable man, the true *vir amabilis ad societatem*.

At the core of character is courage. Sorely afflicted over the years with a complaint for which he knew there could be but the one ending, he faced its many fluctuations with the most *gaillard* courage. Never once did he give utterance to a word of self-pity or complaint, and when the inevitable drew near he found it better

> ". . . to welcome the end of misery
> Than to shun it: a behaviour so noble
> As gives a majesty to adversity."

His living voice is taken from us; but we still retain the lessons he has taught us, by word of mouth and by pen, in the certain knowledge that

> "You cannot call a great soul spent;
> Nothing from life is lost or rent,
> Conserved and hidden though it be
> In the Eternal Energy."

Sir JOHN MCNEE writes: I had known Ernest Finch only as an acquaintance until we came together as visitors of medical schools and inspectors of final examinations for the General Medical Council, but then we worked together in our travels as a team and quickly became close friends. Ernest Finch was a proud citizen of Sheffield and rejoiced in all that happened there. He graduated, with London degrees, when Sheffield took a small place as a training school; and he often acknowledged the debt that he, and Sheffield, owed to the late Sir Arthur Hall, who "made" the Sheffield medical school. Finch, by his early training and inclinations, might easily have turned to physiology or pathology as his life's work, but he saw the need for good surgical practice in Sheffield. Others may speak of his surgical work there, but his interests and influence soon spread far beyond that city. One honorary post which I know gave him the utmost pleasure was his long spell as secretary of the Moynihan Surgical Club, where in its travels he made so many friends at home and abroad.

Shrewd and hard-headed, with a great love for accuracy in detail in everything he did, Ernest Finch made his mark in our profession during a happy lifetime, saddened only in recent years by an illness which would have made lesser men give up at once, but which only seemed to spur him to hasten his activities.

JOHN CAMERON, M.D., D.Sc.

Professor John Cameron, emeritus professor of anatomy at Dalhousie University, Nova Scotia, and a former secretary of the Anatomical Society of Great Britain and Ireland, died at Bournemouth on November 27. He was 87 years of age.

John Cameron was born at Laurencekirk, Scotland, on September 16, 1878, the son of Major David Cameron, of the Gordon Highlanders. Educated at Montrose Academy and the University of Edinburgh, he graduated M.B., Ch.B., with honours, in 1898. His first appointment as an anatomist was as demonstrator in the University of St. Andrews, where he took the degree of D.Sc. in 1904, and where he held a research fellowship from 1902 to 1905. After three years as senior demonstrator in the University of Manchester, he was appointed lecturer in anatomy in the Middlesex Hospital Medical School in 1908. He became a member of the council of the Anatomical Society of Great Britain and Ireland in that year, and was elected the society's secretary for England in 1913. He was an examiner in anatomy at the Universities of St. Andrews and London and at the Royal College of Surgeons. In 1915 he accepted the appointment of professor of anatomy at Dalhousie University, and he remained in Canada until his retirement in 1930. Since then he had been living in Bournemouth. For a time during the first world war he served as a captain in the Canadian Army Medical Corps. He was elected a Fellow of the Royal Society of Edinburgh in 1910.

Professor Cameron wrote extensively on various aspects of the development of the nervous system and published a number of papers in the *Journal of Anatomy*. His M.D. thesis, for which he won a gold medal at Edinburgh, was on the development of the retina. Other papers were concerned with the development of nerve fibres, the development of the optic, auditory, and olfactory nerves, the origin of the pineal body, and the relation of the lamina terminalis to the fornix system. The papers he presented to the Anatomical Society were on a wide variety of subjects, including ancient Egyptian skeletons and various abnormalities in man. His textbook of regional anatomy ran to a third edition in 1931, and he was also the author of a textbook on osteology and arthrology.

G. J. AITKEN, M.B., Ch.B., B.Sc., F.R.F.P.S.

Dr. G. J. Aitken died on December 9 at the Glasgow Royal Infirmary, where he was consultant physician and senior assistant cardiologist. He was 46 years of age.

George James Aitken studied medicine at the University of Glasgow, graduating M.B., Ch.B., with honours, in 1936. Three years before this he had taken the degree of B.Sc. and had undertaken a year's study of pathology under the late Sir Robert Muir. After a brilliant undergraduate career he laid a solid foundation for his later work as a physician by spending two years in house appointments in the Glasgow Western and Glasgow Royal Infirmaries and a further six months as resident at Heathfield (Ayr) Hospital for Infectious Diseases. In 1939 he was appointed assistant physician to the out-patient department at Glasgow Royal Infirmary and Hall tutorial fellow in the department of medicine in the University. He was elected F.R.F.P.S. in 1940.

From 1940 to 1946 he served in the R.A.F. in Britain and in N. Africa as a clinical pathologist, and during this time he wrote several papers on the diagnosis of tropical diseases. On his return from service he rejoined the staff of the Glasgow Royal Infirmary and in 1948 was appointed assistant physician and senior assistant cardiologist. In 1950 he gave the James Watson prize lecture before the Royal Faculty of Physicians and Surgeons of Glasgow, and four years later he was honorary secretary, Section of Cardiology, at the Annual Meeting of the B.M.A. in Glasgow. For the past three years he had been a member of the Central Consultants and Specialists Committee.

J. H. W. writes: George Aitken was a man of many talents who was dedicated to the science and humanity of medicine. Since graduation he had been closely associated with the cardiology department of the Royal Infirmary, Glasgow. His return from war service was at a time when a great forward surge in the progress of cardiology took place, and his was the prepared mind ready to accept the challenge and opportunity.

He was largely responsible for the development of phonocardiography, cardiac catheterization, and other diagnostic aids and of the establishment for use in West of Scotland hospitals of criteria of suitability for operation in cases of rheumatic heart disease. He was a man of powerful build—a mechanical genius capable of building his own machines and tackling the toughest problems—and yet he had a delicacy of touch with the finest of instruments which was the envy of all. He was the true scientist, equipped with an inquiring critical mind, but he had a wealth of understanding and sympathy for others. It was fitting that he should be attracted to the study of cardiovascular disease in children and that his main contributions should be in the field of congenital heart disease. His work on the wide patent duct was an important contribution to the literature. He was in the process of completing a survey of his very considerable experience in congenital heart disease, and it will be a task of love for those who worked with him to ensure that this work is not lost.

George Aitken was a man of wonderful courage who could shake off the rebuffs and disappointments of fate with a shrug of his shoulders. Never was this courage shown more plainly than during his last painful illness when, working to the end, his only thought was to protect his family and his friends. His going is a great loss to medicine and is mourned by all who knew him. He still had so much to give, but if solace there be, it is in the thought that he generously gave of what he had to his colleagues and juniors and he has lit a trail for them to follow. His married life was one of quiet happiness. To his widow and two daughters we offer our deep sympathy.

JAMES McINTOSH, M.D.

Dr. James McIntosh, physician-superintendent of the Western District Hospital, Glasgow, died recently at the age of 54.

James McIntosh was born on January 26, 1906, and graduated M.B., Ch.B. at the University of Glasgow in 1933. Later he was appointed assistant physician to the Eastern District Hospital in Glasgow. He was always concerned about the health of the poorest section of the community and was the joint author of a report on anaemia in the Poor-Law classes of Glasgow. In 1941, shortly after he had proceeded M.D., he joined the R.A.M.C.; while serving in Burma he was mentioned in dispatches in recognition of gallant and distinguished services.

Dr. ALEX. CRAWFORD writes: Dr. James McIntosh will long be remembered for his work in the Western District (Oakbank) Hospital, Glasgow. Originally a Poor Law institution, the sour odour of the "parish" lingered in the gloomy corridors and the grim wards of Oakbank long after the parish council and the Poor Law it administered had ceased to exist. It was difficult to persuade patients to enter Oakbank, for the belief, which was at one time not unsupported by evidence, that only paupers and the incurable aged were treated there was hard to eradicate.

In his all-too-short time as physician-superintendent Dr. McIntosh transformed the hospital, and at the time of his death he had brought it to the point where it promised to become a general hospital as good as any, and no less acceptable to patients than the excellent great teaching hospitals of Glasgow.

This change was brought about not merely by spending money. Dr. McIntosh was kind and courteous to an unusual degree. Indeed, to many he seemed to radiate an aura of goodness; no one who came in contact with him could fail to be impressed by his kindness and the earnestness of his desire to be of service. Especially the friend of the general practitioner, he knew the great difficulty of practice in an old congested industrial area with housing conditions as bad as anywhere in Glasgow and with a high proportion of old chronic sick. Despite his burden of ill-health, a legacy of the war, Dr. McIntosh's help was readily available in hospital or in slum hovel, and no case was too old or too chronic to arouse his interest and compassion. His untimely death is a great personal loss to the many general practitioners in the area served by his hospital. It is on their behalf that this appreciation is written.

J. P. SPENCER WALKER, B.M., B.Ch.

Mr. J. P. Spencer Walker, consulting surgeon to the Sussex Eye Hospital, Brighton, and Horsham Hospital, died on December 7, aged 68.

John Paul Spencer Walker was born at Brighton on January 7, 1892, the only child of the Reverend and Mrs. Spencer Walker, and grandson of Canon Sanderson, headmaster of Lancing College. He was educated at Lancing and Oriel College, Oxford. A fine oarsman, he was deprived of a blue by the first world war. Going on to St. Thomas's Hospital for his clinical training, he graduated B.M., B.Ch. in 1917, and after serving in the Royal Navy returned to St. Thomas's as senior house-surgeon in the ophthalmic department. After holding the post of resident medical officer at the Royal Sussex County Hospital, he was appointed assistant surgeon to the Sussex Eye Hospital in 1921, and at the same time for a few years he was in private general practice with his uncle, Dr. Robert Sanderson, in Hove. He became full consultant in 1930. This was in the days when the Eye Hospital was in its original building in Queen's Road, Brighton. It was Spencer Walker who conceived the plan of building a new hospital, and, largely owing to his efforts, a committee was formed and in 1935 the present Eye Hospital in Eastern Road, Brighton, was opened. This hospital was very dear to him, and, although in the second world war he offered his services to the Royal Navy on more than one occasion, he was obliged to stay in Brighton, and for a period of several months he was the only surgeon on the staff of the hospital. He was particularly interested in orthoptics, which brought him into contact with young people, and he was mainly responsible for the setting up of the orthoptic department at the hospital. In 1940 he was appointed consulting ophthalmic surgeon to the Horsham Hospital, and he was proud of the fact that he was the only non-London man on the consulting staff. He retired from the active staff of his hospitals in 1957 and was honorary consulting surgeon until his death.

A founder member of the Southern Ophthalmological Society, he was its first president in 1945, and he was president of the Brighton and Sussex Medico-Chirurgical Society in 1949. For many years he was on the council of the Faculty of Ophthalmologists. In 1956 he was a vice-president of the Section of Ophthalmology at the Annual Meeting of the B.M.A. in Brighton.

He was an accomplished artist, but a completely natural one, never having had a lesson in his life. He exhibited at the Royal Academy and he derived great pleasure in his love of art, being secretary of the Brighton Arts Club for many years. The present drawings of ocular conditions hanging in the lecture room of the Eye Hospital were done by him when he began lecturing to the nurses over 30 years ago. In addition to his skill as a surgeon and an artist he enjoyed working with his hands; carpentry, french polishing, bricklaying, and photography were amongst his other accomplishments. He loved gardening and beautiful things. Scrupulous in his use of words, he always meant what he said. He was at all times kind and courteous, but shy and retiring. He was an unusual man and will be greatly missed by many friends.

He married late in life Norah Margaret, daughter of Dr. Griffith, and in his marriage he found great happiness. We extend our deep sympathy to his widow.—R. T. T.

G. F. T. SAUNDERS, O.B.E., M.D.

Dr. G. F. T. Saunders, who was formerly a specialist in the Colonial Medical Service, and whose professional life was spent in the Gold Coast, died on November 18 at Kumasi, Ghana, after a motor accident. He was 64 years of age.

George Francis Thomas Saunders was born at Kingston, Co. Dublin, on September 2, 1896. He had a hard time in his youth, but his mother gave him what help she could from her earnings as a domestic servant during his student days: but it was a grim battle with poverty, and he used to say that he had hardly had a square meal for years before he stepped on to an Elder Dempster ship. From Wesley College he went on to Trinity College, Dublin, but at the outbreak of the first world war he joined up as a private in the R.A.M.C., transferring to the Royal Engineers in 1917. He returned to Trinity College to study medicine, graduating M.B., B.Ch., in 1923, and proceeding M.D. in 1926. He joined the Gold Coast medical service in 1928, and soon immersed himself in the uphill task of improving the health of the rural people. His organization of a campaign to control sleeping-sickness met with remarkable success. A highly talented man, he was one of the medical eccentrics who used to find their way into the Colonial Medical Service and whose talents were often wasted through lack of rapport with their superiors. Saunders, fortunately, was in the end given his head, and he was appointed O.B.E. for his services. Shortly before his retirement a paper of his on the diagnosis of human trypanosomiasis was published in this journal in 1952.

Dr. GEORGE L. ALEXANDER writes: Apart from his achievements in his own special field of medicine, George Saunders was a remarkable character. He began to train for the priesthood, but found he had no vocation. Yet to the end there remained something of the priest, or rather, perhaps, of the friar, in him: and consequently many were not wholly at ease in his presence. He would do anything he could to save children from the hell his own early life had been, and he had adopted, or helped to maintain and educate, a number of children, six or more, some at home, some in Ghana.

I first met him in Lawra, in the north-west corner of Ghana, in 1932. In those days he did his travelling on a bicycle with one spare shirt and an odd volume of the *Encyclopaedia Britannica*, and had no need of government rest-houses. Naturally he was sneered at by many as having "gone native": but I think there was more to it than that: he was one of those who achieve purification by reduction of bodily needs. From the medical point of view there was not much to cheer in the Northern Territories then. A devastating epidemic of sleeping sickness was sweeping across them; but, the country being of no commercial importance, there was little money and few staff available. How depressing it was to see nearly half the people of a large village lying around crippled by guinea-worm ulcers and abscesses for lack of a hundred or two pounds for a water supply. Most medical officers regarded posting there as a punishment for having annoyed head office in some way. Yet Saunders was happy to dedicate himself to these fascinating peoples: and on this unpromising foundation he

built up his wonderful organization. Later, when Ashanti, a centre of the cocoa industry, was hit, it was a great deal easier to get the money and staff he needed.

I last met him in 1957, in his home on the Great North Road outside Kumasi, where he conducted a quiet little practice, mostly among his old friends from the north, with time to examine, to think, and to talk with them. In English medical circles in our young days it was considered folly, or confession of failure, to leave the orthodox grooves and sail away to such places, and, I fear, still is in some quarters. Men like George Saunders make nonsense of such notions. They are our finest exports.

H. C. C. VEITCH, M.R.C.S., L.R.C.P.

Dr. Harry Veitch died suddenly at his home at St. Neots, Huntingdonshire, on November 19. He was 69 years of age.

Harry Cecil Craven Veitch was born on June 6, 1891, at Portland, Dorset. Himself the son of a naval officer who later became Fleet Paymaster, he joined the Navy in 1914 while still a student at University College Hospital, and subsequently qualified M.R.C.S., L.R.C.P. in 1915. He saw much active service, and continued in the Navy until 1922. After holding the post of house-surgeon at Bedford County Hospital he joined Dr. Cross in St. Neots, taking over the practice when his partner died. He became surgeon to the Huntingdon County Hospital, where he specialized in ophthalmic work, but he widened his surgical scope and later undertook general surgery and gynaecology. Later still he became obstetric surgeon to the Paxton Park Maternity Hospital, besides continuing his busy general practice. He was one of the older generation of general practitioners who could cope with any emergency in his stride.

Always cheerful and busy, he was very ready to give any help and advice to anyone who asked him, and that advice was always shrewd and sound. For many years secretary of the local panel committee, he was elected chairman of the Huntingdonshire Local Medical Committee in 1948 and continued in this office to his death. From 1945 to 1949 he was chairman of the Cambridge and Huntingdon Division of the B.M.A. and president of the Branch in 1951–2. He had a fund of stories and a pretty wit in telling them, and no medical meeting was complete without his enlivening presence.

Although his later years were saddened by the loss of his son, missing while flying over Burma in 1944, and later still by the loss of his wife, to whom he was devoted, after a long and painful illness, he was sustained by his buoyant character and innate sense of humour, and continued his many and varied activities both in his work and with the Red Cross, of which he was county controller.

In his leisure hours he satisfied his passion for Gilbert and Sullivan by seldom missing any performance that he could possibly attend, whether of a local amateur society or a London production.

His death in his sleep from a coronary thrombosis was the more unexpected as he had made an excellent recovery from an operation two years ago, and he was apparently as fit and active as he had ever been. His sound counsel and cheerful disposition will be greatly missed by his many friends in Huntingdonshire and the neighbouring counties, and their sympathy is extended to his daughter, Mrs. Pullen, of Kingston.

C. A. BIGNOLD, M.B., Ch.B., B.Sc.

Dr. C. A. Bignold, formerly medical officer of health of the County of Ayr, died at his home in Ayr on December 1, aged 75.

Charles Alfred Bignold was born on April 18, 1885, the eldest son of Mr. W. H. Bignold, who was Collector of Customs at Ayr. Educated at Ayr Academy and Edinburgh University, he graduated M.B., Ch.B. in 1909, having first taken a degree in arts. In the first world war he served with the 11th Field Ambulance, 4th Division, and saw much foreign service. He was in the retreat from Mons, in the battles of the Marne, Aisne, and Ypres, and later he served in India after being invalided from France. He was demobilized in 1919 with the rank of major.

Before the war Dr. Bignold had taken the degree of B.Sc. (public health) at Edinburgh, and had served on the staff of the professor of public health at the Usher Institute, Edinburgh. In 1912 he was appointed assistant medical officer of health for Ayrshire, and in 1926 he was promoted to county medical officer and served in that capacity until 1950. He was early in the field of diphtheria immunization, and it was under his guidance that the large modern Central Hospital at Irvine was erected. In the second world war Dr. Bignold was medical officer in charge of the air-raid precautions unit for Ayrshire. Since his retirement he continued his interest in health matters, serving for many years on the board of management of the southern Ayrshire hospitals. For a time he acted as assistant administrative medical officer to the Western Regional Hospital Board.

Dr. Bignold was a quiet man who carried out the duties that fell to his hand without fuss, but most efficiently. His widow died only eleven days after her husband, and they are survived by one son, who is in general practice in Edinburgh, and a daughter, who is a nursing sister at Ayrshire Central Hospital.

Sir GORDON GORDON-TAYLOR, K.B.E., C.B.
M.D., Hon.LL.D., Hon.Sc.D., M.S., F.R.C.S.

The obituary of Sir Gordon Gordon-Taylor was published in the *Journal* of September 10 (p. 807).

J. C. writes: In the winter of 1942 I was sitting in a train at Victoria Station *en route* to the coast when a surgeon rear-admiral entered my carriage. Seeing that I was reading a textbook of biology he inquired whether I proposed to study medicine. When I replied in the affirmative he was keen to know which hospital I proposed to study at. On mentioning the names of two hospitals in which I was interested, he gently inquired whether I had considered the Middlesex, which I had to confess I had not thought about. There then followed a most interesting conversation on a diversity of subjects. In a miraculously short time, it seemed, we arrived at Gillingham, where he informed me he was operating. Before leaving the carriage he gave me his card and suggested I had a look at the Middlesex and used his card as an introduction to the medical-school secretary. In due course I commenced my studies at the Middlesex, and, though I saw him from time to time, I never had further conversation with him. It was typical of this great man that, when I qualified six years later, one of the first letters I received was from Sir Gordon Gordon-Taylor. I understand that in the course of his travels he frequently obtained recruits for the Middlesex, popularly known as Gordon-Taylor's discoveries.

Sir H. MARTIN GREY, Bt., M.R.C.S., L.R.C.P.

Sir H. Martin Grey, Bt., died in Bishop's Stortford on December 12 after a short illness. He was 77 years of age.

Harry Martin Grey was born on March 12, 1882. Son of the late Captain H. G. Grey, R.N., a kinsman of Viscount Grey of Fallodon, he succeeded his brother as fifth baronet in 1957. Educated at Cleveland House, Weymouth, Fauconberge School, Beccles, and St. Bartholomew's Hospital, he qualified in 1908 and early in his career took up radiology. During the first world war Dr. Martin Grey, as he will be remembered by his friends and colleagues, served in the R.A.M.C., retiring with the rank of major. From 1917 to 1919 he was radiologist to the island of Malta. During the nineteen-twenties, while carrying on a private radiological practice in London, he held appointments at the Royal Eye Hospital, Southwark, and Maida Vale Hospital.

Elected honorary radiologist to Hertford County Hospital in 1930, he held this post until the outbreak of the second world war. He was then appointed radiologist to the E.M.S., being posted to Haymeads Hospital, Bishop's Stortford, also acting as wartime radiologist to Bishop's Stortford General Hospital. He had lived in Bishop's Stortford for the past twenty years and retired from medical practice in 1950, seven years before succeeding to the baronetcy.

Handicapped by deafness, Dr. Martin Grey gave of his best. He was a man with a keen sense of his responsibilities and obligations to hospitals and patients, and he never spared himself. Those who worked with him and grew to know him realized that his vocal hesitation and apparently abrupt manner masked a very kindly nature. This year will be the first in which the consultants and darkroom technicians with whom he worked will alike fail to receive the annual Christmas card which he sent to all, irrespective of their status.

Sir Martin Grey married in 1920 Gwladys, daughter of the late William Maxwell, and she survives him. They had no children. His devotion to his wife was plain for all to see. To Lady Grey, who will so sadly feel his loss, we express our deepest sympathy. He is succeeded by his cousin.—W. J. G.

JAMES C. SEYMOUR, M.B., B.S.

The obituary of Dr. James C. Seymour was published in the *Journal* of December 10 (p. 1743).

Mr. F. W. WATKYN-THOMAS writes: We shall never know what science lost by the death of James Seymour. I am not a lenient critic, and I say in all seriousness that in a short 10 years he gave us the best work of the decade on the labyrinthine circulation, and that work, with all that it implied, was only a promise of greater things to come. At the time of his death he was doing a valuable research on some problems of aviation physiology.

Happy in devotion to his work, he was happy in a joy in the simple things of life. He loved our Cumbrian moors and crags. He was a climber, a fisherman, and a natural countryman. I have a happy memory of a chance meeting in the western fells last summer. We spent a cheerful evening disagreeing about the function of the saccule, and coming up from the lake on the next evening I found him handling a tractor on the mountain-side as skilfully and easily as he handled his surgical tools.

It is tragic that we should needlessly have lost so bright a spirit and so brilliant a mind. But whatever the loss to science and the grief to his friends there should be no vain regrets for one who

> ". . . Held heaven in fee
> To gild his dross thereby,
> With knowledge sure that he endure
> A child until he die."

Every year at our Regimental dinner we drink, not to our dead, but "To absent friends." I would commend the thought.

Mr. J. E. A. O'CONNELL writes: As one who had known James Seymour over the 15 years which have passed since he was house-surgeon in the Department of Neurological Surgery of St. Bartholomew's Hospital, I should like to add a small appreciation of his character to the obituary notice which appeared in the *Journal*. As a man he was quiet and reserved, and even in his student days revealed an unusual maturity of outlook. His self-discipline was witnessed by his early rising, capacity for long hours of work, his fastidious approach to eating and drinking, and the regular exercise, especially swimming, which he took to maintain his physical condition. His ability as a physician was shown repeatedly when he returned to neurological surgery, as he did for some weeks every year; he had a fresh approach to clinical problems founded upon his physiological knowledge. His consideration for his patients, based on his quiet faith, amounted almost to devotion—nothing was ever too much trouble to him. As a surgeon he was dexterous and gentle, and in addition possessed those qualities of loyalty and understanding so invaluable in an assistant. As an investigator he early revealed the intellect and imagination necessary clearly to define a problem and the methods by which it may be solved. To this first requisite were added the energy, critical faculty, dexterity, and patience necessary to pursue the investigation to a successful conclusion—with never a thought to publish his results until entirely satisfied with them, and ever ready to make available his unpublished findings to others. He had already made contributions to the neurophysiology of the internal ear and the nervous control of the calibre of cranial and intracranial blood vessels. Had he lived, much of the work upon which he had been engaged would have been published within the next year.

So much that was yet to come from him will now not do so, and his gentle charm remains only in the memory of his friends. His earthly resting-place lies in the Cumberland valley which he had grown to love, near to those dearest to him, close by the river which had so often given him rest and relaxation. He will surely rest in peace.

Medico-Legal

INQUEST: GLIDING ACCIDENT

[FROM OUR LEGAL CORRESPONDENT]

Inquests upon two men killed in a gliding accident were heard on October 4 and 27 at Dunstable before the Coroner for the County of Bedford South District, Mr. J. A. I. Drew. The men involved were John Francis Westhorpe, aged 25, the resident flying instructor at the London Gliding Club, Dunstable, and Peter James Carter, aged 21, a student, of London W.7.

The accident occurred when Westhorpe was instructing Carter, a gliding pupil, in a Sedbergh Glider, on September 30. The particular lesson was a practice stall and recovery, which was performed satisfactorily at a height of 700 to 800 feet (213 to 243 m.): however, the glider immediately made a more severe stall, from which it did not recover, and fell into the ground almost vertically. The wreckage was inspected by officers of the Accidents Investigation Branch of the Ministry of Aviation, who found no evidence of any pre-crash failure of the glider nor any jamming of its control systems. The daily flying certificate and the airworthiness certificate were found properly completed amongst the wreckage. In the opinion of one of these officers, the cause of the crash was that either the pupil had "frozen" on his column through sudden fear, or that the instructor had been incapacitated. The glider had dual controls. If the pupil had "frozen," the instructor ought to have been able to break his grip; but if anything had happened to the instructor the inexperienced pupil might not have noticed it in time, or he might have been unable to take the necessary action in the time available (about 8 seconds). The glider was airborne for between 55 and 60 seconds.

Declaration of Fitness

John Westhorpe had been an assistant instructor in the club since spring, 1958: in the spring of 1959 he became resident instructor. He underwent no medical examination for the club, but, like other members, had to sign a declaration of physical fitness. Although he had a history of epilepsy, he did not declare this, and the club manager had no knowledge of it. He took out a private pilot's licence for powered aircraft in March, 1960, and for this he had to submit to a medical examination. Westhorpe's doctor gave evidence that his patient had been diagnosed as suffering from temporal lobe epilepsy in November, 1952. He had not had a major attack for seven years, nor a minor attack for five years. He had had his last prescription for anti-epileptic drugs on August 2, 1960. Peter Carter had had an operation in 1959 for pneumothorax, from which he made a good recovery.

The necropsy on both men showed that they died of multiple injuries. In addition, in the case of Westhorpe, there was moderately extensive consolidation with abscess formation of tuberculous origin in the right upper lobe of the lung, and the bladder was severely lacerated. The examination of Carter showed no residual signs of the disease for which his operation had been performed.

A police constable who saw the bodies shortly after the crash stated that Westhorpe "had quite a bit of mucous and froth around his lips," and he had urinated. Medical evidence was given that although these symptoms were compatible with an epileptic fit, they were also both explicable by Westhorpe's injuries to the bladder and elsewhere.

In returning a verdict of accidental death, the jury recommended that the attention of the Minister of Aviation be drawn to the evidence in this case.

APPEALS FROM G.M.C. DISCIPLINARY COMMITTEE'S ORDER

[FROM OUR LEGAL CORRESPONDENT]

Dr. Leslie Elgar Gardiner has lodged a petition of appeal against the decision of the Disciplinary Committee of the General Medical Council of May 25[1] directing that his name be erased from the *Register*. The Committee had adjudged him guilty of infamous conduct in a professional respect in that he had advertised for the purpose of obtaining patients or promoting his own professional advantage by writing a book entitled *Faces, Figures, and Feelings*, which included matter directing attention to his skill, knowledge, services, and qualifications, and further that he had acquiesced in the publication of articles containing similar matter in a woman's magazine. Dr. Gardiner's appeal is expected to be heard before the Privy Council next term.

Petition to Adduce Further Evidence

On December 19 Dr. Gardiner appeared in person before the Privy Council to present a petition to be allowed to adduce further evidence on the hearing of his appeal (*The Times*, December 20). Without leave no evidence may be adduced on appeal which was not adduced at the trial. Dr. Gardiner complained that counsel for the G.M.C. at the hearing had quoted from the *British Medical Journal* of April 23[2] putting forward the ostensible views of the B.M.A. on advertising. These were published only one month before his hearing and after all his alleged acts of advertising had occurred. Dr. Gardiner stated that the Association's views were deeply resented by some members of the profession. One important ground of his defence had been that he had based his actions on the examples afforded by the conduct of persons of good repute and competence in his profession. If he had known that counsel for the G.M.C. would put forward controversial proposed standards of an association of doctors overtly divided among themselves, he would have relied on the conduct of the B.M.A. also.

B.M.A. Publications

He petitioned that certain documents, being material published directly or indirectly by the authority of the B.M.A., be admitted as new evidence as showing by practical example, as opposed to vague theoretical recommendations, a fair cross-section of material which the British Medical Association considered it proper for doctors to publish under their names, and to address to the general public in the form of popular literature; and also as further showing the various types of advertising devices, and the considerable usage of such devices, whether advertisements in national publications, order forms, display stands, or other marketing methods, which the Association also felt it proper to cause to be employed for the purpose of ensuring wide public attention and consequent profitable and self-supporting trading for the sale of such publications.

[1] *Brit. med. J. Supplement*, 1960, 1, 364.
[2] Ibid., 1960, 1, 225.

Petition Adjourned

Counsel for the G.M.C., opposing the petition, said that Dr. Gardiner had failed to bring himself within the principle upon which fresh evidence will be admitted on appeal. He had not shown that the fresh evidence was not available at the hearing or that it would have had or been likely to have had a determining influence on the decision.

The Privy Council adjourned the petition to be dealt with by the Board on the hearing of the appeal.

Dr. James Albert de Gregory has appealed to the Judicial Committee of the Privy Council against the decision of the Disciplinary Committee of the G.M.C. to erase his name from the *Register* (*Supplement*, December 10, p. 237).

Medical Notes in Parliament

SMALLPOX VACCINATION IN NYASALAND

[FROM OUR PARLIAMENTARY CORRESPONDENT]

The charges of intimidation that have been reported in connexion with the smallpox outbreak in Nyasaland* were discussed briefly in the House of Lords on a question by Earl WINTERTON on December 15. He asked if the outbreak had abated, how many persons had been vaccinated, and if any action was possible under the laws of Nyasaland to prosecute those who, by intimidation, had attempted to persuade people not to be vaccinated. The Earl of PERTH, Minister of State for Colonial Affairs, told him that the epidemic had not yet subsided. The total number vaccinated was over 480,000. When intimidation involved threats of unlawful action, such as violence to persons or property, or was carried out by unlawful means, including conspiracy, the laws of Nyasaland provided for action to be taken against the offenders. In two instances where medical teams had been hindered by physical intimidation the authorities brought forward cases for trial. One had resulted in the conviction of the principal offenders, and the other was shortly to be heard.

Earl WINTERTON said that a serious charge had been made against Dr. Banda, and his party, that he, being a doctor, and having himself been vaccinated, did his best to persuade his followers to intimidate those who wished to be vaccinated. Would it not be fairer to Dr. Banda to say whether or not this statement was true? The Earl of PERTH, commenting that Dr. Banda was able to take care of himself, as they had seen on various occasions, said he was not aware of any statement that he had made on the lines indicated by Earl Winterton. He added that intimidation was a difficult thing to prove. Where there was a case that could be brought to court the Nyasaland Government would certainly take the necessary action. Viscount ALEXANDER OF HILLSBOROUGH asked if the local authorities had been able to achieve the reasonable target they set themselves in the number of cases dealt with. The Earl of PERTH: To the extent that there has been intimidation, clearly the target has not been fulfilled.

ROAD ACCIDENT FEE FOR HOSPITALS

Lord STONHAM asked the Government on December 14 if they would abolish the obligation on hospitals to collect an emergency fee of 12s. 6d. in respect of persons who required treatment as the result of road traffic accidents. Lord NEWTON, Captain of the Yeomen of the Guard, said that hospitals were entitled to these fees and therefore had a duty to claim them. Any changes in the obligation imposed on vehicle users by the Road Traffic Act to pay these fees on a claim being made would require legislation. This was a matter which the Minister of Health would

*See last week's issue of the *Journal* at pp. 1897 and 1882. A letter this week at p. 1955 is also relevant.

bear in mind at the appropriate time. Lord STONHAM described the imposition as unfair to motorists who were not responsible for the accidents, and costly to the hospitals to collect—at least £5 to £10 in time and money. Lord NEWTON pointed out that it was contained in the National Health Service Act in 1946. He was not promising that it would be abolished, but he was not shutting the door.

Lord STONHAM also suggested that in view of the amount of work falling on hospital staffs from the present system of collecting from insurance companies treatment charges in respect of road accidents they would negotiate an agreement for a lump-sum payment based on premium income. Since the average amount recovered was about £350,000 a year he thought an agreed £250,000 would be a good bargain. Lord NEWTON again told him that legislation would be necessary and the suggestion would be borne in mind at the appropriate time.

QUESTIONS IN THE COMMONS

Strontium and Leukaemia

Mr. R. SORENSEN (Leyton, Lab.) asked the Minister of Health on December 12, as representing the Minister for Science, to what extent an increase in the presence of strontium and leukaemia had been detected in infants, children, young people, and adults, respectively, during the past two years. Mr. ENOCH POWELL stated that the average levels of strontium-90 measured in bone during 1959 as a whole showed some increase on those recorded during 1958 for still-born infants, children, and young people, but there was relatively little change from the first to the second half of 1959. He could only give figures for deaths from leukaemia. In the age-groups 0–4, 5–14, 15–24, and 25 upwards these were 141, 192, 95, and 1,958 in 1958, and were 152, 219, 124, and 2,039 in 1959.

Disinfection of Aircraft

Mr. F. NOEL-BAKER (Swindon, Lab.) asked the Minister what steps he had taken to ensure that all aircraft were properly disinfected and cleared of flies and other insects before or on arrival at United Kingdom airports. Miss EDITH PITT replied that all civil aircraft coming from countries outside the Western European Union and the Republic of Ireland must declare on landing when and where they were last disinfected and cleared of insects. The health authority then decided what further action to require on grounds of health.

Mr. NOEL-BAKER asked for a categorical assurance that the World Health Organization recommendations about disinfestation were being rigidly applied at all British airports. Was the Parliamentary Secretary satisfied with the W.H.O. procedure, and was this country taking advantage of the most up-to-date and effective insecticides? Miss PITT told him that past experience had shown that the risk of introducing infectious diseases by aircraft was very small. Disinfection or disinfestation on arrival in the United Kingdom was not normally necessary, since in some circumstances — for example, yellow-fever areas — international sanitary regulations required, among other measures, the disinfection of the aircraft before departure. In any case no vector-borne quarantinable disease existed in this country, and public-health measures would prevent its spread were it introduced.

Western Hospital, Fulham

Mr. POWELL informed Mr. M. STEWART (Fulham, Lab.) that there were no proposals at present before him for the future of the Western Hospital, S.W.6. Mr. STEWART asked if that meant that it was intended, as originally proposed, to go on with the provision of beds for elderly people at this hospital. Was it a fact that in mid-October the regional board was told to suspend work on the plans for Western Hospital, and that the order was countermanded soon afterwards? Mr. POWELL said in answer to the first part that that was the present intention. However, it was necessary that all postgraduate provision for London should be considered as a whole, and work on that was in progress.

Surgery Design and Organization

Mr. L. PAVITT (Willesden, West, Lab.) asked the Minister if he would consider extending the development unit to include a section to advise family doctors on design and building costs of surgeries and on organization and methods in general practice. Mr. POWELL replied that he had had no request on these lines from the profession, but the department's help and advice were available. The Group Practice Loans Fund Committee advised on the design of group-practice premises. Mr. PAVITT urged him to take the initiative, without waiting for the profession to make a request. If the amount of service given by family doctors could be increased it would save considerable expenditure caused by unnecessary hospitalization, and it would be possible to do just that on the lines suggested in the question. Mr. POWELL said the profession was not unaware of the problem, but he would rather the initiative came from them.

Claims for Specialty Breads

Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) and other M.P.s asked the Minister of Agriculture, Fisheries, and Food on December 15 whether, in view of the recent recommendations of the Food Standards Committee† on specialty breads for which claims were made that they were protein-enriched, or starch-reduced, or described as slimming bread, he would make regulations forbidding the advertising of claims of this nature. Mr. C. SOAMES replied that the interests concerned had been given until February 17 to make representations about the Report on Bread and Flour. He would give full consideration to any representations received before deciding whether to implement the Committee's recommendations.

Mr. NOEL BAKER asked if the "interests concerned" meant the manufacturers, advertising agents, and other advertising bodies. Could the House have an assurance that if their representations did not satisfy the Minister that the committee had made a mistake he would take drastic action? Mr. SOAMES replied that representations were open to a wide range of interests. He must leave himself free to consider them before he made a statement. Dr. STROSS said the misrepresentation of fact of this kind was grossly unfair to the public. Was it enough merely that representations should be made? Why should the Minister not help actively? Mr. SOAMES: "I will. I have received the report and it has been published. I have given until February 17 for representations to be made, and I will then make up my mind on the matter and make a statement."

Psychiatric Examinations in Prison

Mr. L. ABSE (Pontypool, Lab.) asked the Home Secretary if he was aware that prison medical officers lacking a recognized psychiatric diploma were regularly submitting reports on the sanity of accused persons to the courts, and what steps he was taking to increase the number of prison medical officers who held a diploma in psychological medicine. Mr. R. A. BUTLER said that few prison medical officers who submitted reports to court on the mental condition of inmates possessed a recognized psychiatric diploma, though all had experience in the diagnosis of mental disorder and the majority were approved by local health authorities for the purposes of Section 28 of the Mental Health Act, 1959. In recruiting prison medical officers, weight was given to the possession of a diploma in psychological medicine, and encouragement was given to medical officers in post to take the diploma wherever possible.

Reports Given to Prosecution

Mr. ABSE stated in another question that persons in custody charged with murder were being compelled to submit

†See *Journal*, December 3, p. 1659.

to psychiatric examination by prison medical officers, and the facts so obtained were supplied to the Director of Public Prosecutions. He asked the Home Secretary to give instructions that no psychiatric examination of an accused person charged with murder should take place, and no report be given to the Director of Public Prosecutions, except with the consent of the accused or his legal advisers. Mr. BUTLER answered that it had for long been the established practice for a report on the mental condition of any prisoner charged with murder to be furnished by the prison medical officer to the court through the Director of Public Prosecutions, who supplied a copy to the defence. The Royal Commission on Capital Punishment approved this practice, but recommended that such prisoners should in future be examined by an independent psychiatrist of standing as well as by an experienced member of the prison medical service. The Government accepted this recommendation. Mr. Butler saw no reason to disturb the existing arrangements, which have been generally accepted as being necessary and desirable in the interests of justice.

Poliomyelitis in Scotland

Dr. J. DICKSON MABON (Greenock, Lab.) asked the Secretary of State for Scotland on December 6 how many persons over 25 years of age had contracted poliomyelitis in Scotland during 1959, and to the nearest convenient date in 1960; how many of these cases were of the paralytic form; and how many persons died from poliomyelitis. Mr. J. S. MACLAY stated that in 1959 in Scotland there were four accepted notifications of poliomyelitis in persons aged 25 and over, all of them of the paralytic form. In 1960, up to November 26, there were two notifications of poliomyelitis in the same age-group; one of these was of paralytic form. Three deaths from poliomyelitis took place in 1959, two being of persons aged 25 and over; no deaths had occurred this year up to September 30.

Universities and Colleges

UNIVERSITY OF OXFORD

In Congregation on December 10, 1960, the following degrees were conferred:

D.M.—R. M. Bannerman.

B.M.—W. J. Appleyard, T. H. D. Arie, L. R. C. Bain, J. W. Baker, H. P. Berg, D. P. G. Bolton, H. M. B. Busfield, J. E. Cawdery, J. R. W. Christie Brown, Sylvia N. Clayton, R. V. Clements, J. M. Gumpel, R. G. Hett, Pamela F. Hull, P. Husband, *J. Kenwright, M. A. Lee, T. S. Low-Beer, I. G. McGill, A. K. McKinlay, Anne C. Maddocks, T. W. Meade, *S. R. Meadow, *J. S. Meyrick, T. N. Miller, *J. Millward, S. H. Milton, D. H. Myers, Elizabeth J. E. Neale, J. L. Nicholas, Gillian M. Roberts, C. Rowlatt, G. E. G. Sladen, J. S. Smith, G. S. Spathis, J. B. P. Stephenson, Gillian R. Sutton, R. A. L. Sutton, C. E. Taylar, Anne M. Waring, C. White, *D. L. Wingate, J. B. Wood.

*In absence.

The Martin Wronker Prize in Medicine for 1960 has been awarded to John Lincoln Duffield, B.A. (Christ Church).

UNIVERSITY OF ABERDEEN

At a Graduation ceremony held on December 14, 1960, the following degrees were conferred:

M.D.—Eleanor M. Adams (with commendation).

M.B., CH.B.—M. L. G. Addison, A. Bremner, G. McK. Bruce, D. S. Gill, G. Jamieson, R. Mercer, Audrey F. Stewart, Mary M. Sutherland.

UNIVERSITY OF EDINBURGH

At a meeting of the University Court held on December 12, 1960, Dr. Bruce Mackay was appointed Lecturer and Dr. E. M. Chinnan, Assistant in the Department of Anatomy.

Dr. G. P. B. Boissard has resigned from the appointment of Lecturer in the Department of Bacteriology, his resignation to take effect from September 30, 1961.

UNIVERSITY OF DUBLIN

SCHOOL OF PHYSIC, TRINITY COLLEGE

The following medical degrees and diplomas were conferred on December 8, 1960:

M.D.—F. L. Willington.

M.B., B.CH., B.A.O.—A. D. S. K. Allen, E. F. Brown, Judith A. Bryan, D. D. Duncan, A. N. Dunn, J. G. G. Eglinton, Celia F. T.-W. Fiennes, J. J. Gorman, J. D. McCarter, Sheila P. McGuinness, Bohdan M. Meeson, Denise R. Millin, R. A. H. Mooney, J. R. Press, P. J. W. M. Sang, R. E. Snow, Margot V. Thomas, Deirdre M. Verling.

L.M., L.CH., L.A.O.—A. Redman.

SCHOOL OF PHYSIC, TRINITY COLLEGE

D. J. Bradley and G. B. Plunkett have passed in the examination for Part I of the Diploma in Psychological Medicine.

UNIVERSITY OF LONDON

Professor A. Bradford Hill, F.R.S., has resigned from the Chair of Medical Statistics at the London School of Hygiene and Tropical Medicine, his resignation to take effect from September 30, 1961.

The following have been recognized as teachers of the University in the subjects indicated in parentheses: *Royal Free Hospital School of Medicine*, Dr. Edith Gilchrist (Anaesthetics). *Institute of Ophthalmology*, Mr. D. P. Greaves and Mr. P. D. Trevor-Roper (Ophthalmology). *Institute of Urology*, Mr. D. I. Williams (Surgery (Urology)).

The title of Professor of Oral Medicine has been conferred on Mr. R. V. Bradlaw in respect of his post at the Institute of Dental Surgery; and the title of Professor of Biophysics as applied to Medicine on Dr. L. F. Lamerton in respect of his post at the Institute of Cancer Research, Royal Cancer Hospital.

UNIVERSITY OF MANCHESTER

The following candidates have satisfied the examiners at the examinations indicated:

M.D.—H. W. Ashworth, E. G. Dryburgh, T. G. Ramsell, C. F. H. Vickers.

FINAL M.B., CH.B.—D. Ashcroft, P. Asquith, A. J. Barson, V. D. Brim, A. G. Brown, S. G. W. Gough, D. E. Harrison, G. A. Hope, D. G. Johnson, Hazel I. Keith, I. C. McInnes, P. Mills, P. F. Norman, Lynda M. Tye, A. Westerman, R. S. Whittaker.

DIPLOMA IN PUBLIC HEALTH.—Angela M. M. Manning, Lydia McMurdo, D. S. Ross, P. Sukavachana.

UNIVERSITY OF WALES

WELSH NATIONAL SCHOOL OF MEDICINE

The following candidates have been approved at the examination indicated:

M.B., B.CH.—Elizabeth R. M. Archer, P. G. Cunningham-Davis, D. G. Daniels, B. E. Deere, M. D. Edwards, J. N. P. Hughes, R. H. Hughes, C. D. Isaacs, K. Jayasinghe, Marlene M. Jones, T. T. Jones, Margaret M. L. Lord, S. N. Nirsimloo, M. J. C. Povey, B. A. Stratford, A. C. Williams.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on December 8, 1960, with Sir Arthur Porritt, President, in the chair, Lord Kindersley was admitted to the Court of Patrons, after a citation had been given in his honour by Sir James Paterson Ross, Bt., Past President.

Professor Digby Chamberlain, of Leeds, was appointed Bradshaw Lecturer for 1961.

Mr. G. T. Hankey was awarded the John Tomes Prize for the period 1957–9 for clinical research, and Professor A. I. Darling the Charles Tomes Lectureship for 1961.

The Hallett Prize was presented to Dr. J. L. Mercer, of St. Thomas's Hospital Medical School, and the Begley Prize to Dr. Joseph Brown, of King's College Hospital Medical School.

Diplomas of Fellowship were granted to the following successful candidates:

C. M. Ruben, A. E. Steel, J. H. F. Batstone, S. K. Bosher, D. C. Gardner, R. A. James, H. J. Waldeck, J. G. Jeffreys, W. M. Mee, E. E. Denman G. C. W. Baker, B. G. Andrews, G. R. E. Roberts, Molly E. Wakely, A. W. F. Lettin, T. C. E. Mbanefo, A.-B. L. Gulati, C. Wastell, A. Cort, G. N. McG. Orr, S. G. Ramaiya, A. J. de Bruin, P. D. Livingstone, B. P. Samanta, H. Kramer, D. J. Adams, A. Bates, I. F. Maclaren, R. K. McRae, H. C. Puri, D. D. Sumariwalla, P. J. Chesterman, A. A. Kazim, J. P. Masterton, C. R. Fenton, B. G. Haggart, D. W. M. Haw, Hon Fah Ho, J. G. Mander, T. N. Shanmugalingam, T. Sussman, J. W. P. Bradley, G. G. Dinning, Earl Ming-Teh Lu, G. W. Crock, D. L. Crosby, D. D. Foster, R. W. Goonewardene, A. H. Grabham, J. M. S. Hague, M. B. Heywood-Waddington, C. T. Howe, J. A. Hunt, E. O'G. Kirwan, A. E. Mody, A. E. J. Mullins, S. S. Reddy, C. J. C. Renton, I. G. Schraibman, L. Sivaraman, M. J. Betty, G. J. Bougher, L. J. Caust, B. C. Cohney, G. A. G. Decker, K. M. Dickinson, J. R. P. Gibbons, D. U. Hay, D. W. Hossack, J. B. Laine, D. J. McAuliffe, R. A. Owen, B. Y. Pai, H. Poirier, D. M. Ritchie, G. R. Thoms, D. L. Annetts, B. R. Bahl, P. M. Binns, F. J. Collins, S. R. Duke, H. M. H. El-Sherif, W. M. P. Fennell, D. C. Glenn, M. C. Green, W. G. Harris, P. McR. Higgins, C. N. Hudson, J. N. Kille, R. Lenaghan, C. J. H. Logan, G. Lynch, B. McKibbin, P. D. Madhok, H. R. Magee, P. M. Meffan, G. J. Ormandy, W. H. Reid, R. L. Rothwell-Jackson, C. E. Rowell, L. Rozner, P. M. Scott, B. R. Shah, H. L. McI. Smith, A. P. Wyatt, H. Ud-Deen Ahmed, C. W. P. Canagaretna, J. K. Chaudhry, Eugene Poh Hwye Chu, S. L. Johari, K. F. King, Franklin Wang-Pong Li, The Hon. William S. Pease, N. M. A. Rogers, J. A. Russell, R. T. Southwood, J. C. Taraporvala, M. V. S. Valiathan, P. J. Venter, I. Smith, M. F. Stranc, V. C. Talwalker.

After the meeting the Robert Jones Lecture was delivered by Mr. H. J. Seddon on "The Manchester Ship Canal and the Colonial Frontier."

Vital Statistics

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

Measles	Week Ending Dec. 3	Dec. 10
Lancashire	1,902	**1,790**
Liverpool C.B.	221	**250**
Manchester C.B.	127	**142**
Oldham C.B.	151	**128**
Yorkshire West Riding	798	**637**
Bradford C.B.	195	**169**
Leeds C.B.	125	**118**
Glamorganshire	233	**324**
Swansea C.B.	110	**187**
Dysentery		
Cheshire	41	**23**
Hoylake R.D.	32	**11**
Kent	7	**24**
Broadstairs and St. Peter's U.D.	1	**13**
Lancashire	116	**76**
Liverpool C.B.	22	**13**
Eccles M.B.	18	**24**
London	50	**39**
Middlesex	24	**39**
Edmonton M.B.	10	**21**
Nottinghamshire	34	**28**
Carlton U.D.	15	**15**
Surrey	4	**19**
Epsom and Ewell M.B.	1	**12**
Yorkshire West Riding	99	**93**
Bradford C.B.	23	**29**
Huddersfield C.B.	19	**14**
Leeds C.B.	26	**23**
Monmouthshire	10	**38**
Newport C.B.	0	**29**
Glasgow	94	**101**

London Statistics

The population of the administrative County of London in 1959 was 3,225,000, slightly less than in the previous year. But the birth rate of 17.2 per 1,000 population was higher than for many years past. 10.41% of total live births in London were illegitimate. This rate has risen from 7.1 in 1954 to its present figure, though the illegitimacy rate for the whole of England and Wales rose only from 4.7 to 5.1 during that time. In his annual report for 1959, from which these figures are taken, Dr. J. A. Scott, Medical Officer of Health to the L.C.C., points out that London has a lower proportion of married women than other parts of the country and it also offers attractive facilities to unmarried mothers—antenatal care, anonymity, and support from moral welfare organizations.

London had 75 cases of diphtheria in 1959, much the highest figure since 1950. The notifications of dysentery (3,571) and enteric fever (84) were also relatively high. By the midpoint of 1959 about two-thirds of London children up to 16 years of age had been vaccinated against poliomyelitis. The incidence rate of poliomyelitis in unvaccinated children was about seven times that in the vaccinated. Although infestation with lice or nits is far less common than it used to be, about 5 schoolchildren out of every 400 examined at the annual comprehensive health surveys were found to be verminous. 544 cases of scabies were notified during the year.

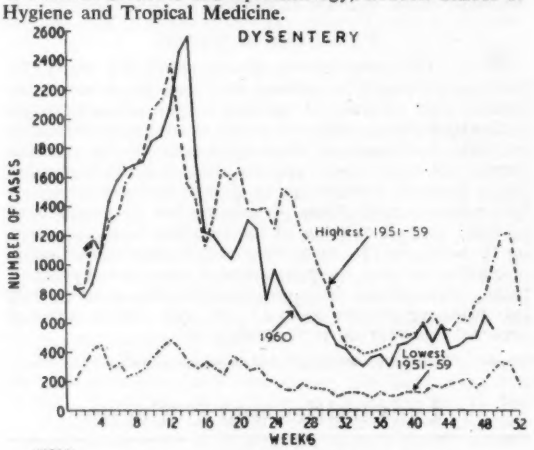
The number of men (11,722) and of women (2,599) who were treated for gonorrhoea at London out-patient clinics in 1959 was more than double the number who came for treatment ten years ago.

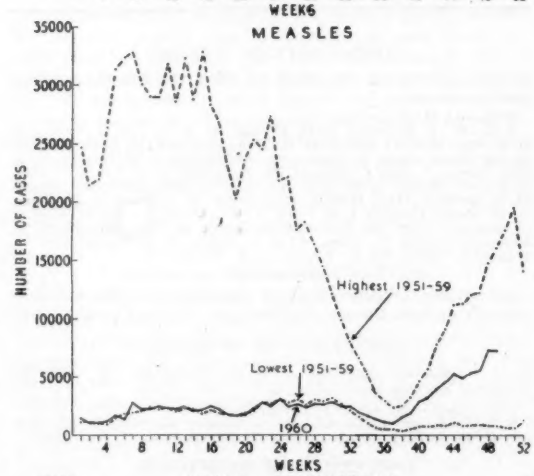
Road Accidents in October

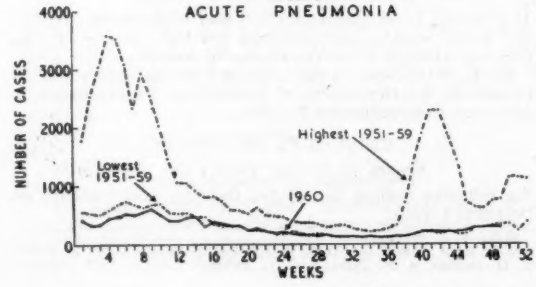
The 670 deaths from road accidents in October was the highest figure so far for any month in 1960—being 15 more than in October last year. The number of children killed was 61—4 more than in October, 1959—bringing the total child deaths on the roads this year to 641, or 64 more than in the same period of 1959. The total number of casualties—killed and injured—on the roads in October was 31,740, an increase of 522, or nearly 2% compared with last year. Motor traffic is estimated to have increased by 4% over the same period.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.



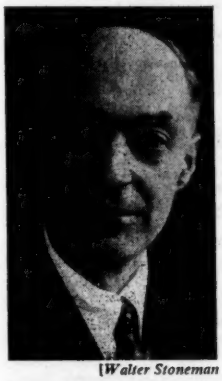




Medical News

Royal Society's New Gold Medal

The Trustees of the Leverhulme Trust Fund have marked the occasion of the Royal Society's Tercentenary by the award of a gold medal. Under the terms of the offer the medal is "for award by the Society, every three years, to the individual who in the opinion of its Council shall have made the most significant contribution in the field of pure or applied chemistry or engineering including chemical engineering. The medal, which will be in gold, will be accompanied by a monetary award of five hundred pounds."



[*Walter Stoneman*

The Council has made the first award of the medal to Sir CYRIL HINSHELWOOD, O.M., F.R.S., who retired as President of the Royal Society on November 30 last, for his outstanding contributions to physical chemistry.

Royal Society

Sir LINDOR BROWN, biological secretary of the Royal Society and Waynflete professor of physiology at Oxford University, is among those appointed to be vice-presidents of the Society for the coming year.

Chair of Medicine, Westminster Medical School

Dr. M. D. MILNE, lecturer in medicine at the Postgraduate Medical School of London and honorary consultant physician to the Hammersmith Hospital, has been appointed to the London University chair of medicine tenable at Westminster Medical School.

Dr. Milne, who is aged 45, qualified in medicine in 1939 at the University of Manchester. From 1940 to 1946 he served in the Royal Army Medical Corps, chiefly in field units with the Eighth Army in North Africa and Italy. After the war he held junior posts in the professorial unit of medicine at the Manchester Royal Infirmary, and from 1950 to 1952 was lecturer in medicine at the University of Manchester. He gained his M.D. in 1951, and was elected F.R.C.P. in 1958. He has held his present posts since 1952. Dr. Milne is chiefly interested in renal and metabolic disease and in the biochemical aspects of pharmacology. He has written papers on acute oliguric renal failure, various renal diseases associated with aminoaciduria, primary aldosteronism, parathyroid function, and the pharmacology of anti-hypertensive drugs.

Central Sterilizing Club

The second meeting of the Central Sterilizing Club was held at Downing College and Addenbrooke's Hospital, Cambridge, on December 19 and 20. The programme included papers on "The C.S.D. at Addenbrooke's Hospital," "The Sterilization Reference Laboratory," "Methods of Cleaning," "Distribution," "Paper as a Barrier against Bacterial Contamination," and "The Steam Disinfection of Blankets: a Central Supply Problem?" as well as group discussions and demonstrations. The honorary secretary of the club is Dr. J. REVANS, Highcroft, Romsey Road, Winchester, Hants.

Oral Polio Vaccine

The Wellcome Foundation Ltd. has announced that during the summer it discontinued for a time the production of the killed, or "Salk," variety of poliomyelitis vaccine in favour of large-scale development of attenuated living virus vaccine. Tests are nearly complete on large batches of all three types (Sabin strains) of this material.

Labelling of Medicinal Preparations

A memorandum, *Labelling Procedure for Compounded Medicinal Preparations*, which gives guidance on the procedure to be followed in devising labels and titles for new preparations, has been prepared and recommended to their members by the Association of British Pharmaceutical Industry, the Proprietary Association of Great Britain, and the Association of Public Analysts.

East Germany Woos Doctors

In an effort to stop the continuing exodus of doctors, dentists, and chemists from East Germany, the policy-making committee of the East German Communist Party has promised them considerable privileges. Those for doctors include the right of State doctors to have private practices, and the formation of a medical trade union. According to figures recently published in West Germany, 2,054 doctors, 683 dentists, and 158 veterinary surgeons left East Germany in two years, as well as many nurses, chemists, and trained assistants (*The Times*, December 21).

Combined Colleges' Bronze Medal

The Combined Colleges' Bronze Medal, donated by the Royal College of Surgeons of England, the Royal College of Physicians of London, and the Royal College of Obstetricians and Gynaecologists, will be awarded in 1961 by the Medical Group of the Royal Photographic Society to any person of any nationality, whether a member of the Society or not, for an outstanding example of photography in the service of medicine and surgery. Work submitted or detailed nominations for the award should be received by the Honorary Secretary of the group, 16 Prince's Gate, London S.W.7, by September 30.

The Medal for 1960 has been awarded to Dr. DAVID RUHE, associate professor of public health, Kansas University Medical School and director of the audio-visual department there, for two films on "Emergency Airways for Tricothyroid Puncture and Tracheotomy."

British Association of Plastic Surgeons

The following have been appointed to serve as officers of the B.A.P.S. for 1961: *president*, Air Commodore G. H. MORLEY; *immediate past president*, Mr. P. H. JAYES; *honorary treasurer*, Mr. R. P. OSBORNE; *honorary editor*, Mr. A. B. WALLACE; *honorary secretary*, Mr. JOHN WATSON; *members of council*, Mr. R. J. V. BATTLE, Mr. C. R. MCLAUGHLIN, Mr. I. F. K. MUIR, Mr. E. W. PEET, Mr. J. S. TOUGH; *overseas representative on council*, Mr. N. A. M. PETERSEN, South Africa.

Sully Hospital, Glamorgan

A new cardiac laboratory at Sully Hospital, Glamorgan, was opened by Sir CLEMENT PRICE THOMAS, the president of the Welsh National School of Medicine, on December 19. The Welsh Regional Hospital Board has equipped the department with cine-radiography apparatus which includes an 11-in. and a 5-in. image intensifier; a closed-circuit television system is used for cardiac catheterization with the

5-in. image intensifier. Other equipment in the laboratory includes a six-channel direct-writing recorder with pressure transducers, and equipment for photometric blood-gas analysis and radio-isotope measurements.

National Survey of Air Pollution

A new national survey to obtain as accurate a record as possible of air pollution throughout the country has been accepted by the Standing Conference of Co-operating Bodies for the Investigation of Atmospheric Pollution. The first part of the survey will cover towns selected by statistical methods to give national overall figures of pollution by sulphur and sulphur dioxide (volumetric method), and the second part covers all other towns which are making measurements now or may do so in the future. An analysis of the results will be published as they become annually available.

International Academy of Proctology 1960–1 Award

The academy is awarding its annual cash prize ($100) and certificate of merit for the best unpublished contribution on proctology or allied subjects. Details are obtainable from Dr. A. J. CANTOR, International Academy of Proctology, 147-41 Sanford Avenue, Flushing 55, New York, U.S.A. The closing date is February 1.

Guild of St. Luke, SS. Cosmas and Damian

The Guild has elected the following officers: *master*, Mr. J. V. O'SULLIVAN; *honorary secretary*, Dr. J. W. DIGNAN; *honorary treasurer*, Dr. W. C. TURNER.

H. J. McCurrich Prize, 1962

The Regional Hospitals' Consultants and Specialists Association is offering the H. J. McCurrich Prize of 100 guineas for an essay based on a medical or surgical topic. Qualified hospital staff up to and including senior registrars may enter, and the essay should be written during tenure of office in hospitals in England and Wales. Details from the Secretary, 47 Lincoln's Inn Fields, London W.C.2. Closing date, December 15, 1961.

Change of Title

From January, 1961, the *Journal of the American Pharmaceutical Association, Scientific Edition*, will be renamed *Journal of Pharmaceutical Sciences*, while the *Journal of the American Pharmaceutical Association, Practical Pharmacy Edition*, will be known as the *Journal of the American Pharmaceutical Association*.

People in the News

Professor R. J. LAST, professor of applied anatomy at the Royal College of Surgeons, was among the distinguished visitors from the United Kingdom who attended the centenary celebrations of the King Edward Medical College, Lahore (*Journal*, December 10, p. 1748).

Mr. T. HOLMES SELLORS is attending as a guest at the Indian Association of Surgeons in Poona in December, and lecturing in some of the major centres, under the auspices of the British Council, during January.

COMING EVENTS

Institute of Dermatology.—Exhibition, January 9–27, by Mr. R. J. LUNNON, A.I.B.P., F.R.P.S., "Direct Ultra-violet Photography of the Skin," St. John's Hospital for Diseases of the Skin, Lisle Street, Leicester Square, London W.C.2.

Watson Smith Lecture.—Dr. LOUIS FORMAN, "The Reaction of the Skin to Certain Metals," January 10. For details see advertisement p. 34.

Walker Lecture.—Professor M. L. ROSENHEIM, "Chronic Pyelonephritis," January 11, 5 p.m., Maurice Bloch Lecture Theatre, Royal Faculty of Physicians and Surgeons. Glasgow.

Marc Daniels Lecture.—Dr. CLIFFORD HOYLE, "The Prognosis of Pulmonary Sarcoidosis," January 12. For details see advertisement p. 34.

Family Planning Association.—Training courses for general practitioners. See advertisement p. 34.

SPECIALIST JOURNALS AND ABSTRACTS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

BRITISH JOURNAL OF PHARMACOLOGY AND CHEMOTHERAPY

The Antitubercular Properties of a Series of Thiols and Sulphides. P. Acred and D. M. Brown.
The Antitubercular Activity of 3-Acetylthiopropylene Sulphide and 3-(2-Furoylthio)propylene Sulphide. P. Acred, D. M. Brown, and D. Wright.
Interaction Between Histamine and Dichloroisoproterenol, Hexamethonium, Pempidine, and Diphenhydramine in Normal and Reserpine-treated Heart Preparations. P. F. Mannaioni.
Neuromuscular Blockade by Streptomycin and Dihydrostreptomycin. M. N. Jindal and V. R. Deshpande.
The Effect of Levallorphan Tartrate and of Adiphenine Hydrochloride on the Antidiuretic Action of Morphine and Nicotine. H. Schnieden.
The Effect of Diet on the 5-Hydroxytryptamine Content of the Small Intestine and Other Organs in Rats and Mice. T. J. Sullivan.
The Distribution of 5-Hydroxytryptamine and Adenosinetriphosphate in Cytoplasmic Particles of the Dog's Small Intestine. W. H. Prusoff.
The Anticholinesterase Activity of Some Antiadrenaline Agents. Helen Boyd, V. Chang, and M. J. Rand.
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SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Wednesday, January 4

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. H. G. Hanley: Disorders of Micturition in the Female.

Thursday, January 5

INSTITUTE OF NEUROLOGY.—5 p.m., Dr. Carl Pearson (California): Some Biochemical Studies in Muscle Disease.

ROYAL PHOTOGRAPHIC SOCIETY OF GREAT BRITAIN: MEDICAL GROUP.—At 16 Princes Gate, London S.W., 6.30 for 7 p.m., Mr. Charles Engel, F.R.P.S., and Mr. John Brace, B.Sc.: Closed Circuit Television in Medical Diagnosis, Research and Teaching.

Friday, January 6

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—(1) 3.30 p.m., clinical discussion for general practitioners. Dr. C. H. Edwards: Vertigo and Differential Diagnosis. (2) 5.30 p.m., Mr. N. Asherson: Some Uncommon Diseases of Childhood.

Saturday, January 7

MIDLAND THORACIC SOCIETY.—At Birmingham Medical Institute, 3 p.m., Short papers. Mr. J. M. Sanderson: Results of Major Surgery for Pulmonary Tuberculosis; Dr. A. Clark Penman and Dr. P. G. Arblaster: Simple Lung Function Tests and Their Clinical Application.

BIRTHS, MARRIAGES, AND DEATHS

Aitken.—On December 9, 1960, at the Royal Infirmary, Glasgow, George James Aitken, M.B., Ch.B., F.R.F.P.S., of 18 Newlands Road, Glasgow, aged 47.
Bignold.—On December 1, 1960, at 2 Park Terrace, Ayr, Charles Alfred Bignold, M.B., Ch.B.
Cremin.—On November 28, 1960, in Joyce Green Hospital, Dartford, Kent, John Joseph Cremin, M.B., B.Ch., of London Road, Crayford, Kent, aged 69.
Curtis.—On December 11, 1960, George Herbert Curtis, M.R.C.S., L.R.C.P., L.D.S., of 17 Clarence Gate Gardens, London N.W.
Dickie.—On December 4, 1960, at Perth Royal Infirmary, Ronald Stevenson Dickie, M.B., Ch.B., Colonel, late R.A.M.C., retired, late of Strathtay, Perthshire.
Doig.—On December 3, 1960, at Nyeri, Kenya, Kenneth Alan Crawford Doig, M.R.C.S., L.R.C.P., Major, R.A.M.C., retired.
Garrett.—On December 3, 1960, Philip Gell Garrett, M.B., B.S., D.P.H., of Uplands, Henfield, Sussex.
Sinclair.—On November 29, 1960, at White House, Coleorton, Leicester, John Sinclair, M.B., Ch.B., aged 55.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Premedication for Bronchography

Q.—*What reasonable premedication is desirable before the administration of 4% lignocaine for bronchography in an out-patient department? If signs of toxicity develop, what is the best treatment? Is there any means of testing the patient beforehand for possible intolerance? What would be maximum safe dosage to use in ml.? Has any safer local anaesthetic yet been manufactured?*

A.—A suitable premedication for bronchography in an out-patient department would consist of atropine and a suitably small dose of a sedative such as pentobarbitone or similar drug. Toxic symptoms with lignocaine are very rare, but they have occurred. Treatment consists in ensuring good ventilation and oxygenation until recovery. If convulsions should occur, very small doses of thiopentone will help to control them. Toxic symptoms should be regarded as due to overdose; there is no means other than care in dosage for guarding against this possibility beforehand. The maximum safe dose of lignocaine in an adult lies between 0.5 and 1 g. If 4% lignocaine is chosen, therefore, no more than, say, 15 ml. should be made up or used. The "safety" of a local anaesthetic in clinical use is more related to the way it is handled than to its inherent pharmacological properties. Limitation of dose (both in concentration and in volume) and the prevention of the rapid entry of the drug into the circulation by suitable techniques are important factors. From this point of view the clinical "safety" of lignocaine is on a par with such drugs as carbocaine and procaine. No "safer" drugs than these have yet been manufactured.

Bland, Low-fat Diet

Q.—*I have a patient aged 44 who is overweight. He has had symptoms of peptic ulceration in the past and at present. He has had two proved coronary thromboses and is at present on long-term anticoagulants. I wish to give this man a diet to reduce his weight, of reasonable blandness to prevent the onset of dyspepsia, and low in animal fats. Will you please prescribe such a diet?*

A.—The following is a sample diet sheet.

Breakfast.—Porridge (strained), 3 tablespoonfuls. One egg, poached or lightly boiled; or one 1 oz. (28 g.) rasher of grilled bacon; or steamed white fish, a small helping. One thin slice of toast with margarine from daily ration. Tea with milk from daily ration.

11 a.m.—6 oz. (170 ml.) milk from ration.

Mid-day.—Small helping of lean meat (all visible fat removed); or chicken; or tripe; or rabbit. Purée of carrot; or turnip; or spinach; or average helping of fresh green peas. Junket, milk from ration. Orange juice or rose-hip syrup.

Tea.—One thin slice of toast with margarine from ration or two rich-tea biscuits. Finely chopped lettuce heart; purée of tomato with skins and seeds removed; portion of "St. Ivel" cheese. Tea with milk from ration.

Evening meal.—Choice of lean meat, chicken, steamed fish, or rabbit, as at mid-day meal. Choice of vegetables *en purée*. Three water biscuits with portion of "St. Ivel" or other light cheese. Orange juice.

Before retiring.—6 oz. (170 ml.) milk from ration.

Daily rations.—Milk (fresh, skimmed) 1¼ pints (0.85 l.). Margarine (vegetable oil—e.g., kosher—with vitamins added) ¾ oz. (21.3 g.).

Total calories.—Approximately 1,200.

The following should be avoided:

Sugar.; jam; marmalade; honey; syrup; sweets; chocolate; tinned fruit; cakes; scones; buns; pastry; puddings; thick sauces; gravies; salad cream; ice-cream; fried or greasy food; highly spiced food; rough food, such as nuts; seedy or stringy fruit or vegetables; pickles; vinegar; sauces; alcohol; and toasted cheeses.

Faecal Impaction with Incontinence

Q.—*Frequent and offensive loose bowel motions are very usual during the last days or weeks of life. They add intolerably to the burden of the dying and to their attendants and are a common reason for hospital care being sought. What is the cause, and can anything be done?*

A.—This condition is frequently caused by faecal impaction. Clearance of the bowel by enemata and rectal washouts will often modify the condition and make nursing easier and the patient more comfortable. The cause is an inability to empty the bowel properly, even though diarrhoea, or incontinence, rather than constipation is the obvious symptom. A rectal examination will reveal the true situation.

Colouring Saturated Solution of Sodium Sulphate

Q.—*To 40 oz. (1.1 l.) of a saturated solution of sodium sulphate I added 2 drachms (7 ml.) of liquor rubra. The sodium sulphate very rapidly separated out. Why was this? Could you tell me how to colour a saturated solution of sodium sulphate?*

A.—Many dyes are not pure substances of uniform composition. They may also contain components which form a colloidal solution, not a true solution, on dissolving in water. The addition of a saturated solution of sodium sulphate to such a dye solution would cause precipitation of colloidal matter by a "salting out" action. This is probably the case with liquor rubra, since this is prepared from Bordeaux B or azorubrum. The last standard for this dye was in the 1949 edition of the *B.P.C.*, and this required only 65% of the pure compound to be present.

It has been replaced in subsequent editions of the *Codex* by liquor amaranth. This does not give a precipitate with saturated solution of sodium sulphate and would be quite suitable for colouring it. About 0.5% v/v of the solution of amaranth, *B.P.C.*, gives a good red colour. Other dyes giving a deep red colour are magenta and "edicol supra rose" (I.C.I.). A pale red is given by eosin (strength in each case 0.5% v/v of a 1% w/v solution). Liquor tartrazinae co., *B.P.C.* (0.5% v/v), gives a lemon yellow colour. The solution containing magenta has given a precipitate after three days. The others remain clear.

Vectorcardiography

Q.—*What are the advantages of vectorcardiography? Does it show anything which an E.C.G. does not, and, if so, in what cases would it be indicated?*

A.—Spatial vectorcardiography is an attempt to represent in three dimensions the electrical activity of the heart. It depends on the use of surface electrodes of the same kind as those used to record the ordinary ("scalar") E.C.G., though they are not placed in the same positions. It does not record data fundamentally different from those recorded by the scalar E.C.G., but it displays the data in a different manner. Bipolar leads are arranged so that they "look at" the heart from three directions—from the front, from above, and from the side. By combining these views a three-dimensional image can be constructed, much as an architect can visualize a house by looking at "plan" and "elevation."

As a research tool the vectorcardiograph has increased understanding of the way in which the various scalar E.C.G. patterns are produced. As a diagnostic aid it has, so far, been less helpful. It can distinguish between the various kinds of R.S.R.′ pattern in the right chest leads. It can sometimes show clear evidence of posterior infarction when

the scalar-lead patterns are doubtful. In many cases of ostium-primum atrial septal defect the V.C.G. is radically different from that seen with an ostium-secundum defect. In theory, at least, it could distinguish between changes that are due to altered position of the heart from changes due to other causes. These are its chief clinical uses at the moment.

Noise and Vision

Q.—*A middle-aged man suffering from a stationary hypermetropia complains that his vision becomes blurred rhythmically in response to the ringing tone of a telephone; it also occurs as a temporary loss of accommodation with any loud, sudden noise. Is this a well-known condition?*

A.—This is not a well-known condition. Any strong sensory stimulus tends to inhibit reception of other sensory stimuli. A strong auditory stimulus can be used to induce some degree of anaesthesia, for example, and is, I understand, being used for this purpose in the United States. This inhibition of pain presumably occurs in the higher centres and is probably not associated with accommodative changes.

Hot Mud-packs

Q.—*What is the principle of hot mud-pack treatment for "rheumatism" as carried out at spas? Is it safe for a man aged 59 who has no signs of cardiovascular abnormality?*

A.—A hot mud-pack is merely a form of applying moist heat, and is used in the treatment of painful joints at many spas. There is no evidence to support the contention that the various ingredients of the mud used have any therapeutic effect. Provided thermal sensation is normal and there is no abnormality of the skin, there are no contraindications to this form of treatment.

Persisting Leucopenia in Pernicious Anaemia

Q.—*A patient with pernicious anaemia has a red blood count of about 5 million, but her white blood count is about 2,700, with normal proportions of white cells. She seems quite unable to resist any current infection that may be about. Is there any way of raising her white blood count?*

A.—Adequate treatment of a patient with pernicious anaemia is usually followed by a return to normal values for the white blood cells as well as the red cells, haemoglobin, and platelets. Occasionally, however, the total white cell count does not go up to within the usually accepted normal range after cyanocobalamin therapy. When liver and stomach preparations were the usual forms of treatment for pernicious anaemia a good brisk response took place in all the cellular elements of the blood, and a persisting leucopenia was much more rarely observed.

The patient might be given a preparation of a relatively crude liver extract such as ½ oz. (14.2 g.) of proteolysed liver orally daily. Most cases will respond to this form of treatment but not to the highly purified liver extracts for parenteral use. The response probably does not depend solely on cyanocobalamin or folic acid.

Cortisone and Operations

Q.—*There appears to be some confusion about the effect of hydrocortisone and allied substances on minor operative procedures. I understand that patients undergoing a prolonged course of cortisone should have their dose increased considerably before general anaesthesia. Should similar precautions be taken before minor surgical procedures, such as tooth extractions, under local anaesthesia?*

A.—There is indeed some confusion over this problem, largely owing to inability to predict the response of the individual patient.[1] It is, however, well recognized that patients receiving corticosteroids may be incapable of responding adequately even to minor stress, and fatalities have been reported following operation. Moreover, such patients are sensitive to the effects of drugs, anaesthetics, and blood loss. Full recovery of adrenal function may not occur for up to two years after stopping corticosteroids. With these facts in mind, it is necessary to increase the dosage during the operative period, though this should be moderate rather than considerable, as stated in the question, because of the possibility—admittedly remote—of delayed healing and spread of infection. Suitable regimes were referred to in an annotation in the *Journal*.[2] In the case of minor operations such as tooth extraction under local anaesthesia it is wise to double the dose for 48 hours and to warn the patient to report any untoward reaction at once.

REFERENCES

1 Salassa, R. M., Bennett, W. A., Keating, F. R., jun., and Sprague, R. G., *J. Amer. med. Ass.*, 1953, **152**, 1509.
2 *Brit. med. J.*, 1959, **1**, 1464.

NOTES AND COMMENTS

Plantar Warts and Public Baths.—Dr. F. GROARKE (Romford, Essex) writes: In the reply to a question relating to plantar warts ("Any Questions?" November 26, p. 1616) the following is stated: "Plantar warts and molluscum contagiosum are contagious . . . and are spread through public baths." Could I know what evidence exists in confirmation of the statement that they are spread through public baths?

OUR EXPERT replies: Dr. Groarke is correct in implying that there is no absolute proof, in the sense of the infective agent having been cultured from baths as in the case of ringworm infection of the feet. Unfortunately the infective agent of warts and mollusca remains very elusive. There is much circumstantial evidence,[1 2] particularly in relation to epidemics in schools, supporting the hypothesis, but there can be no certainty until cultural proof is obtained.

REFERENCES

1 Lyell, A., *Lancet*, 1955, **2**, 349.
2 Low, R. C., *Edinb. med. J.*, 1946, **53**, 657.

Napkin-rash.—Dr. MARY N. M. PAULIN (Belfast) writes: Once again I am forced to write to you on the subject of napkin-rash to disagree with your expert ("Any Questions?" November 26, p 1616). I think napkin-rash is due to the interaction of nitrifying bacteria in the napkin and the urine resulting in the formation of ammonia which burns the skin. The mother of a baby with a sore bottom nearly always says, "The water smells very strong, doctor." The cure is not to boil the napkins—bacteria in napkins cannot be destroyed by ordinary domestic boiling, but they can be destroyed by ordinary domestic bleaching agents. I recommend that the napkins should be soaked overnight in bleach and then washed in the ordinary way with as many rinses as you like. The baby's bottom should be protected with a very liberal layer of zinc and castor oil cream. In the vast majority of cases this will cure the sore bottom which is in the raw and bleeding state.

Correction.—The figure given on p. 1817, *Journal*, December 17, for additional registrations with the British United Provident Association should have read 38,423 and not 369,248, which represents all registrations.

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